# Metastatic progression via biased random walks on a cancer network

#### P.K. Newton

Viterbi School of Engineering & Department of Mathematics University of Southern California

P.K. Newton Metastatic progression on networks

ヘロト 人間 ト ヘヨト ヘヨト

## Outline



#### Goals

The autopsy data set

#### The Markov model

- The transition matrix
- The state-vector
- The steady-state

#### Building the lung cancer network

- A constrained optimization problem
- The trained matrix
- The lung cancer network
- Unbiased diffusion process
- 5

#### Biased random walks on the network

- Individual trajectories
- Mean first-passage times
- Singular value decomposition

.≣⇒

< 🗇

Conclusions

#### Goals of the model:

- Build a computational 'platform' for Monte Carlo simulations of cancer progression
- Start by building this for the generic 'average' patient, focusing on lung cancer
- Then build the model for other types of cancer for comparison purposes
- Compare with individual patient histories
- Use model to quantify predictions
- Use model to perform 'tests'

イロト イポト イヨト イヨト

#### Goals of the model:

- Build a computational 'platform' for Monte Carlo simulations of cancer progression
- Start by building this for the generic 'average' patient, focusing on lung cancer
- Then build the model for other types of cancer for comparison purposes
- Compare with individual patient histories
- Use model to quantify predictions
- Use model to perform 'tests'

くロト (過) (目) (日)

#### Goals of the model:

- Build a computational 'platform' for Monte Carlo simulations of cancer progression
- Start by building this for the generic 'average' patient, focusing on lung cancer
- Then build the model for other types of cancer for comparison purposes
- Compare with individual patient histories
- Use model to quantify predictions
- Use model to perform 'tests'

くロト (過) (目) (日)

#### Goals of the model:

- Build a computational 'platform' for Monte Carlo simulations of cancer progression
- Start by building this for the generic 'average' patient, focusing on lung cancer
- Then build the model for other types of cancer for comparison purposes
- Compare with individual patient histories
- Use model to quantify predictions
- Use model to perform 'tests'

イロト 不得 とくほ とくほう

#### Goals of the model:

- Build a computational 'platform' for Monte Carlo simulations of cancer progression
- Start by building this for the generic 'average' patient, focusing on lung cancer
- Then build the model for other types of cancer for comparison purposes
- Compare with individual patient histories
- Use model to quantify predictions

Use model to perform 'tests'

ヘロト ヘ戸ト ヘヨト ヘヨト

#### Goals of the model:

- Build a computational 'platform' for Monte Carlo simulations of cancer progression
- Start by building this for the generic 'average' patient, focusing on lung cancer
- Then build the model for other types of cancer for comparison purposes
- Compare with individual patient histories
- Use model to quantify predictions
- Use model to perform 'tests'

イロト イポト イヨト イヨト

## DiSibio & French (2008)

#### 3827 untreated patients (1914-1943)



P.K. Newton Metastatic progression on networks

ヘロン 人間 とくほ とくほう

э

## DiSibio & French (2008)

#### 3827 untreated patients (1914-1943)

#### METASTATIC SITE

		1		- and -	4		at a	lal ada	*	\$		40	1 ,	and	and a second	1	**	and a state	Contral.	le anno 1	4	and a second	1	• .	200	1	Res	3	ore	1	1	
		4	4	1	4	4	10	7	4	4	3	4	2	3	3	8	8	4	4	~	2	*	41	4	4	4	*		R	2	Sa.	
adrenal	6	1	3	0	2	0	1	0	0	1	2	1	3	3	4	0	1	1	0	0	1	0	0	3	0	2	1	0	1	0	0	31
2000	29	3	4	1	1	0	1	2	2	2	8	1	7	5	7	1	0	1	2	2	4	0	0	2	1	3	0	0	1	0	0	61
Appendix	2	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	•
pile duct	34	3	3	0	0	0	0	2	0	0	4	1	10	15	2	0	0	1	0	5	2	0	0	0	0	2	1	0	0	0	0	51
aladans	183	11	20	0	0	0	2	0	2	9	30	1	25	80	45	1	2	2	1	7	4	3	2	1	4	3	0	0	1	0	0	256
BODA	35	4	15	1	1	0	3	0	2	2	18	1	6	8	8	0	1	3	0	1	6	1	0	6	0	1	0	0	0	0	0	
Branchial	10	0	1	0	0	0	0	0	1	1	3	0	2	9	4	0	0	0	0	0	1	0	0	0	0	0	0	0	2	0	0	24
Branst	432	149	213	17	42	54	36	19	22	40	247	11	218	230	277	8	53	49	52	59	158	1	0	124	12	52	17	0	35	33	7	2235
Careta	418	23	36	10	1	0	10	3	7	19	94	11	97	232	133	8	24	6	2	37	11	0	0	5	12	13	2	0	2	1	7	806
00100	123	9	2	0	1	0	2	2	0	7	15	4	35	42	19	6	3	9	0	20	1	0	0	1	3	1	1	0	3	4	0	190
papterne	11	0	0	0	1	0	0	0	0	0	2	0	1	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7
Recobergue	129	6	6	0	0	0	2	0	3	4	19	1	21	70	22	0	0	4	3	4	8	0	1	2	1	2	2	0	2	0	0	183
\$5°	10	3	1	0	1	0	0	1	4	1	4	0	6	0	3	0	0	2	0	1	2	0	0	2	1	0	0	1	0	1	0	34
Gall-dasz	35	5	3	1	0	0	3	1	0	1	9	2	18	21	13	3	0	8	0	4	2	0	0	2	3	2	1	0	0	0	0	102
R1. Armers	62	18	20	2	4	1	2	1	8	8	30	5	21	23	26	1	1	9	1	6	10	1	1	3	4	3	2	0	1	0	0	212

P.K. Newton Metastatic progression on networks

#### Key features of data set

- 50 combined primary or metastatic sites
- 39 primaries, 11 metastatic sites that are not primary sites
- Data set is large, but not comprehensive
- Each row gives ensemble metastatic distribution from a given primary
- These distributions represent the 'long-time' steady-state
- Patients are untreated males and females

くロト (過) (目) (日)

#### Key features of data set

- 50 combined primary or metastatic sites
- 39 primaries, 11 metastatic sites that are not primary sites
- Data set is large, but not comprehensive
- Each row gives ensemble metastatic distribution from a given primary
- These distributions represent the 'long-time' steady-state
- Patients are untreated males and females

ヘロト ヘアト ヘビト ヘビト

#### Key features of data set

- 50 combined primary or metastatic sites
- 39 primaries, 11 metastatic sites that are not primary sites
- Data set is large, but not comprehensive
- Each row gives ensemble metastatic distribution from a given primary
- These distributions represent the 'long-time' steady-state
- Patients are untreated males and females

ヘロト ヘアト ヘビト ヘビト

#### Key features of data set

- 50 combined primary or metastatic sites
- 39 primaries, 11 metastatic sites that are not primary sites
- Data set is large, but not comprehensive
- Each row gives ensemble metastatic distribution from a given primary
- These distributions represent the 'long-time' steady-state
- Patients are untreated males and females

ヘロン 人間 とくほ とくほ とう

#### Key features of data set

- 50 combined primary or metastatic sites
- 39 primaries, 11 metastatic sites that are not primary sites
- Data set is large, but not comprehensive
- Each row gives ensemble metastatic distribution from a given primary
- These distributions represent the 'long-time' steady-state
- Patients are untreated males and females

ヘロン 人間 とくほ とくほ とう

#### Key features of data set

- 50 combined primary or metastatic sites
- 39 primaries, 11 metastatic sites that are not primary sites
- Data set is large, but not comprehensive
- Each row gives ensemble metastatic distribution from a given primary
- These distributions represent the 'long-time' steady-state
- Patients are untreated males and females

ヘロト ヘアト ヘビト ヘビト

## Metastatic distribution from all primaries

#### Overall metastatic distribution



ヘロト ヘ戸ト ヘヨト ヘヨト

## Metastatic distribution from lung cancer primary

#### $\vec{v}_{T}$ : The target 'statistical' steady-state distribution (27 sites)



イロト イポト イヨト イヨト

э

Building the lung cancer network Biased random walks on the network Conclusions The transition matrix The state-vector The steady-state

## Defining the transition matrix

$$\vec{v}_{k+1} = \vec{v}_k A$$
, (k = 0, 1, 2, ....)

- 50 locations that are either primaries or metastatic sites
- A is a 50 × 50 transition matrix
- Rows sum to 1
- Entries are all primary and metastatic sites
- These will be the 'nodes' of our network model
- The nodes will be connected by directed edges
- Edge weightings will be determined by solving an optimization problem

Goals The autopsy data set **The Markov model** Building the lung cancer network

Biased random walks on the network Conclusions The transition matrix The state-vector The steady-state

## Defining the transition matrix

$$\vec{v}_{k+1} = \vec{v}_k A$$
, (k = 0, 1, 2, ....)

- 50 locations that are either primaries or metastatic sites
- A is a 50 × 50 transition matrix
- Rows sum to 1
- Entries are all primary and metastatic sites
- These will be the 'nodes' of our network model
- The nodes will be connected by directed edges
- Edge weightings will be determined by solving an optimization problem

The transition matrix The state-vector The steady-state

## Defining the transition matrix

$$\vec{v}_{k+1} = \vec{v}_k A$$
, (k = 0, 1, 2, ....)

- 50 locations that are either primaries or metastatic sites
- A is a 50  $\times$  50 transition matrix
- Rows sum to 1
- Entries are all primary and metastatic sites
- These will be the 'nodes' of our network model
- The nodes will be connected by directed edges
- Edge weightings will be determined by solving an optimization problem

The transition matrix The state-vector The steady-state

## Defining the transition matrix

#### The Markov chain model

$$\vec{v}_{k+1} = \vec{v}_k A$$
, (k = 0, 1, 2, ....)

- 50 locations that are either primaries or metastatic sites
- A is a 50 × 50 transition matrix

### Rows sum to 1

- Entries are all primary and metastatic sites
- These will be the 'nodes' of our network model
- The nodes will be connected by directed edges
- Edge weightings will be determined by solving an optimization problem

The transition matrix The state-vector The steady-state

## Defining the transition matrix

$$\vec{v}_{k+1} = \vec{v}_k A$$
, (k = 0, 1, 2, ....)

- 50 locations that are either primaries or metastatic sites
- A is a 50  $\times$  50 transition matrix
- Rows sum to 1
- Entries are all primary and metastatic sites
- These will be the 'nodes' of our network model
- The nodes will be connected by directed edges
- Edge weightings will be determined by solving an optimization problem

Conclusions

The transition matrix The state-vector The steady-state

## Defining the transition matrix

$$\vec{v}_{k+1} = \vec{v}_k A$$
, (k = 0, 1, 2, ....)

- 50 locations that are either primaries or metastatic sites
- A is a 50  $\times$  50 transition matrix
- Rows sum to 1
- Entries are all primary and metastatic sites
- These will be the 'nodes' of our network model
- The nodes will be connected by directed edges
- Edge weightings will be determined by solving an optimization problem

Goals The autopsy data set **The Markov model** Building the lung cancer network

Building the lung cancer network Biased random walks on the network Conclusions The transition matrix The state-vector The steady-state

## Defining the transition matrix

$$\vec{v}_{k+1} = \vec{v}_k A$$
, (k = 0, 1, 2, ....)

- 50 locations that are either primaries or metastatic sites
- A is a 50  $\times$  50 transition matrix
- Rows sum to 1
- Entries are all primary and metastatic sites
- These will be the 'nodes' of our network model
- The nodes will be connected by directed edges
- Edge weightings will be determined by solving an optimization problem

Goals The autopsy data set **The Markov model** Building the lung cancer network

Biased random walks on the network Conclusions The transition matrix The state-vector The steady-state

## Defining the transition matrix

$$\vec{v}_{k+1} = \vec{v}_k A$$
, (k = 0, 1, 2, ....)

- 50 locations that are either primaries or metastatic sites
- A is a 50  $\times$  50 transition matrix
- Rows sum to 1
- Entries are all primary and metastatic sites
- These will be the 'nodes' of our network model
- The nodes will be connected by directed edges
- Edge weightings will be determined by solving an optimization problem

Building the lung cancer network Biased random walks on the network Conclusions The transition matrix The state-vector The steady-state

#### The 50 nodes that make up our network

#	Name	#	Name	
1	Adrenal	26	Omentum	
2	Anus	27	Ovaries	
3	Appendix	28	Pancreas	
4	Bile Duct	29	Penis	
5	Bladder	30	Pericardium	
6	Bone	31	Peritoneum	
7	Brain	32	Pharynx	
8	Branchial Cyst	33	Pleura	
9	Breast	34	Prostate	
10	Cervix	35	Rectum	
11	Colon	36	Retroperitoneum	
12	Diaphragm	37	Salivary	
13	Duodenum	38	Skeletal Muscle	
14	Esophagus	39	Skin	
15	Eye	40	Small Intestine	
16	Gallbladder	41	Spleen	
17	Heart	42	Stomach	
18	Kidney	43	Testes	
19	Large Intestine	44	Thyroid	
20	Larynx	45	Tongue	
21	Lip	46	Tonsil	
22	Liver	47	Unknown	
23	Lung	48	Uterus	
24	Lymph Nodes (reg)	49	Vagina	
25	Lymph Nodes (dist)	50	Vulva	

P.K. Newton

Metastatic progression on networks

Building the lung cancer network Biased random walks on the network Conclusions The transition matri The state-vector The steady-state

## State-vector representation

#### $\vec{v}_0$ : The initial state-vector

- Represents the distribution of primary tumors (and our level of certainty)
- $\vec{v}_0 = (1, 0, 0, 0, ....)$ : Primary tumor located in Adrenal gland
- \$\vec{v}\_0 = (0, 0, 0, 0, ..., 1, 0, 0, 0, ...)\$: Primary tumor located in Lung
- $\vec{v}_0 = (1/50, 1/50, 1/50, ....)$ : Complete lack of information on location of primary tumor
- *v*<sub>0</sub> = (1/2, 0, 0, 0, ..., 1/2, 0, 0, 0, ...): Primary tumor located in Adrenal and/or Lung

ヘロン ヘアン ヘビン ヘビン

Building the lung cancer network Biased random walks on the network Conclusions The transition matri: The state-vector The steady-state

## State-vector representation

#### $\vec{v}_0$ : The initial state-vector

- Represents the distribution of primary tumors (and our level of certainty)
- $\vec{v}_0 = (1, 0, 0, 0, ....)$ : Primary tumor located in Adrenal gland
- \$\vec{v}\_0 = (0, 0, 0, 0, ..., 1, 0, 0, 0, ...)\$: Primary tumor located in Lung
- $\vec{v}_0 = (1/50, 1/50, 1/50, ....)$ : Complete lack of information on location of primary tumor
- *v*<sub>0</sub> = (1/2, 0, 0, 0, ..., 1/2, 0, 0, 0, ...): Primary tumor located in Adrenal and/or Lung

イロト 不得 とくほ とくほとう

Building the lung cancer network Biased random walks on the network Conclusions The transition matri The state-vector The steady-state

## State-vector representation

#### $\vec{v}_0$ : The initial state-vector

- Represents the distribution of primary tumors (and our level of certainty)
- $\vec{v}_0 = (1, 0, 0, 0, ....)$ : Primary tumor located in Adrenal gland
- $\vec{v}_0 = (0, 0, 0, 0, ..., 1, 0, 0, 0, ...)$ : Primary tumor located in Lung
- $\vec{v}_0 = (1/50, 1/50, 1/50, ...)$ : Complete lack of information on location of primary tumor
- *v*<sub>0</sub> = (1/2, 0, 0, 0, ..., 1/2, 0, 0, 0, ...): Primary tumor located in Adrenal and/or Lung

ヘロン ヘアン ヘビン ヘビン

Building the lung cancer network Biased random walks on the network Conclusions The transition matri: The state-vector The steady-state

## State-vector representation

#### $\vec{v}_0$ : The initial state-vector

- Represents the distribution of primary tumors (and our level of certainty)
- $\vec{v}_0 = (1, 0, 0, 0, ....)$ : Primary tumor located in Adrenal gland
- $\vec{v}_0 = (0, 0, 0, 0, ..., 1, 0, 0, 0, ...)$ : Primary tumor located in Lung
- \$\vec{v}\_0\$ = (1/50, 1/50, 1/50, ....): Complete lack of information on location of primary tumor
- *v*<sub>0</sub> = (1/2, 0, 0, 0, ..., 1/2, 0, 0, 0, ...): Primary tumor located in Adrenal and/or Lung

イロト 不得 とくほ とくほとう

э
Building the lung cancer network Biased random walks on the network Conclusions The transition matri The state-vector The steady-state

## State-vector representation

## $\vec{v}_0$ : The initial state-vector

- Represents the distribution of primary tumors (and our level of certainty)
- $\vec{v}_0 = (1, 0, 0, 0, ....)$ : Primary tumor located in Adrenal gland
- $\vec{v}_0 = (0, 0, 0, 0, ..., 1, 0, 0, 0, ...)$ : Primary tumor located in Lung
- $\vec{v}_0 = (1/50, 1/50, 1/50, ...)$ : Complete lack of information on location of primary tumor
- \$\vec{v}\_0 = (1/2, 0, 0, 0, ..., 1/2, 0, 0, 0, ...)\$: Primary tumor located in Adrenal and/or Lung

ヘロト 人間 ト ヘヨト ヘヨト

Building the lung cancer network Biased random walks on the network Conclusions The transition matrix The state-vector The steady-state

## Metastatic progression

### State-vector dynamics

$$\vec{v}_1 = \vec{v}_0 A$$
  
 $\vec{v}_2 = \vec{v}_1 A = \vec{v}_0 A^2$   
 $\vec{v}_3 = \vec{v}_2 A = \vec{v}_0 A^3$ 

.

.

$$\vec{v}_{k+1} = \vec{v}_k A = \vec{v}_0 A^{k+1}$$

P.K. Newton Metastatic progression on networks

ヘロマ 人間マ 人間マ 人間マ

э

Building the lung cancer network Biased random walks on the network Conclusions The transition matrix The state-vector The steady-state

# The steady-state 'statistical' distribution

 $\vec{v}_{\infty}$ :  $k \to \infty$ 

$$\vec{v}_{\infty} = \lim_{k \to \infty} \vec{v}_0 A^k$$
$$\vec{v}_{\infty} = \vec{v}_{\infty} A$$
$$\vec{v}_{\infty} (A - I) = 0$$

- $\vec{v}_{\infty}$  is an eigenvector of A corresponding to eigenvalue 1
- Since A is stochastic, must have at least one steady-state
- Find entries of *A* so that  $\vec{v}_{\infty} \equiv \vec{v}_T$

Building the lung cancer network Biased random walks on the network Conclusions The transition matrix The state-vector The steady-state

# The steady-state 'statistical' distribution

 $\vec{v}_{\infty}$ :  $k \to \infty$ 

$$ec{v}_{\infty} = \lim_{k o \infty} ec{v}_0 A^k$$
  
 $ec{v}_{\infty} = ec{v}_{\infty} A$   
 $ec{v}_{\infty} (A - I) = 0$ 

- $\vec{v}_{\infty}$  is an eigenvector of A corresponding to eigenvalue 1
- Since A is stochastic, must have at least one steady-state
- Find entries of *A* so that  $\vec{v}_{\infty} \equiv \vec{v}_T$

Building the lung cancer network Biased random walks on the network Conclusions The transition matrix The state-vector The steady-state

# The steady-state 'statistical' distribution

 $\vec{v}_{\infty}$ :  $k \to \infty$ 

$$ec{v}_{\infty} = \lim_{k o \infty} ec{v}_0 A^k$$
  
 $ec{v}_{\infty} = ec{v}_{\infty} A$   
 $ec{v}_{\infty} (A - I) = 0$ 

- $\vec{v}_{\infty}$  is an eigenvector of A corresponding to eigenvalue 1
- Since A is stochastic, must have at least one steady-state
- Find entries of *A* so that  $\vec{v}_{\infty} \equiv \vec{v}_T$

Building the lung cancer network Biased random walks on the network Conclusions The transition matrix The state-vector The steady-state

# The steady-state 'statistical' distribution

 $\vec{v}_{\infty}$ :  $k \to \infty$ 

$$egin{aligned} ec{v}_{\infty} &= \lim_{k o \infty} ec{v}_0 A^k \ ec{v}_{\infty} &= ec{v}_{\infty} A \ ec{v}_{\infty} (A-I) &= 0 \end{aligned}$$

•  $\vec{v}_{\infty}$  is an eigenvector of A corresponding to eigenvalue 1

• Since A is stochastic, must have at least one steady-state

• Find entries of *A* so that  $\vec{v}_{\infty} \equiv \vec{v}_T$ 

Building the lung cancer network Biased random walks on the network Conclusions The transition matrix The state-vector The steady-state

# The steady-state 'statistical' distribution

 $\vec{v}_{\infty}$ :  $k \to \infty$ 

$$ec{v}_{\infty} = \lim_{k o \infty} ec{v}_0 A^k$$
  
 $ec{v}_{\infty} = ec{v}_{\infty} A$   
 $ec{v}_{\infty} (A - I) = 0$ 

- $\vec{v}_{\infty}$  is an eigenvector of A corresponding to eigenvalue 1
- Since A is stochastic, must have at least one steady-state
- Find entries of *A* so that  $\vec{v}_{\infty} \equiv \vec{v}_T$

Building the lung cancer network Biased random walks on the network Conclusions The transition matrix The state-vector The steady-state

# The steady-state 'statistical' distribution

 $\vec{v}_{\infty}$ :  $k \to \infty$ 

$$ec{v}_{\infty} = \lim_{k o \infty} ec{v}_0 A^k$$
  
 $ec{v}_{\infty} = ec{v}_{\infty} A$   
 $ec{v}_{\infty} (A - I) = 0$ 

- $\vec{v}_{\infty}$  is an eigenvector of A corresponding to eigenvalue 1
- Since A is stochastic, must have at least one steady-state
- Find entries of *A* so that  $\vec{v}_{\infty} \equiv \vec{v}_T$

イロト 不得 とくほ とくほとう

A constrained optimization problem The trained matrix The lung cancer network Unbiased diffusion process

# Constrained linear optimization problem

Find the entries  $a_{ii}$  of the transition matrix A, subject to:

$$\vec{v}_T(A-I)=0$$

• Constraints:  $0 \le a_{ij} \le 1$ ;  $\sum_{j=1}^{50} a_{ij} = 1$ .

イロト 不得 とくほ とくほとう

A constrained optimization problem The trained matrix The lung cancer network Unbiased diffusion process

# Constrained linear optimization problem

Find the entries  $a_{ij}$  of the transition matrix A, subject to:

$$\vec{v}_T(A-I)=0$$

• Constraints: 
$$0 \le a_{ij} \le 1; \sum_{j=1}^{50} a_{ij} = 1.$$

イロト イポト イヨト イヨト

A constrained optimization problem The trained matrix The lung cancer network Unbiased diffusion process

# 'Training' the matrix

 $A_j$  is a 50  $\times$  50 transition matrix

$$ec{v}_T(A_j-I) 
eq 0$$
  
 $ec{v}_\infty^{(j)}(A_j-I) = 0$ 

 $\vec{r}_i$ : The residual vector

$$ec{v}_T(A_j-I)=(ec{v}_T-ec{v}_\infty^{(j)})(A_j-I)\equivec{r}_j$$

イロン 不同 とくほ とくほ とう

3

A constrained optimization problem The trained matrix The lung cancer network Unbiased diffusion process

# 'Training' the matrix

 $A_j$  is a 50  $\times$  50 transition matrix

$$ec{v}_T(A_j-I) 
eq 0$$
  
 $ec{v}_\infty^{(j)}(A_j-I) = 0$ 

## $\vec{r_i}$ : The residual vector

$$ec{v}_{\mathcal{T}}(\mathcal{A}_j-\mathit{I})=(ec{v}_{\mathcal{T}}-ec{v}_{\infty}^{(j)})(\mathcal{A}_j-\mathit{I})\equivec{r}_j$$

ヘロア 人間 アメヨア 人口 ア

ъ

A constrained optimization problem The trained matrix The lung cancer network Unbiased diffusion process

# 'Training' the matrix

#### Two-step process

• Step 1: Approximate 
$$(A_0, j = 0)$$

• Step 2: Iterate 
$$(A_j, j = 1, 2, ...)$$

Goal: Drive the residual norm ||*r*<sub>j</sub>||<sup>2</sup> to zero as *j* → ∞.
 ||(*v*<sub>T</sub> − *v*<sub>∞</sub><sup>(j)</sup>)||<sup>2</sup> → 0

イロト 不得 とくほ とくほ とう

3

A constrained optimization problem The trained matrix The lung cancer network Unbiased diffusion process

# 'Training' the matrix

#### Two-step process

- Step 1: Approximate  $(A_0, j = 0)$
- Step 2: Iterate (*A<sub>j</sub>*, *j* = 1, 2, ...)
- Goal: Drive the residual norm ||*r*<sub>j</sub>||<sup>2</sup> to zero as *j* → ∞.
   ||(*v*<sub>T</sub> − *v*<sub>∞</sub><sup>(j)</sup>)||<sup>2</sup> → 0

イロト 不得 とくほ とくほ とう

3

A constrained optimization problem The trained matrix The lung cancer network Unbiased diffusion process

# 'Training' the matrix

#### Two-step process

- Step 1: Approximate ( $A_0$ , j = 0)
- Step 2: Iterate (*A<sub>j</sub>*, *j* = 1, 2, ...)
- Goal: Drive the residual norm  $\|\vec{r}_j\|^2$  to zero as  $j \to \infty$ .

• 
$$\|(\vec{v}_T - \vec{v}_\infty^{(j)})\|^2 \to 0$$

イロン 不同 とくほ とくほ とう

# Finding a 'good' $A_0$

A constrained optimization problem The trained matrix The lung cancer network Unbiased diffusion process

## Our first approximation

- For each primary in data set, use raw numbers to fill out rows
- Normalize each of those rows by dividing by sum
- Fill out entries for the remaining empty rows with 'unbiased' values  $a_{ij} = 1/50$
- A<sub>0</sub> constructed this way is a stochastic transition matrix
- But  $\vec{v}_T(A_0 I) \neq 0$

ヘロア 人間 アメヨア 人口 ア

# Finding a 'good' $A_0$

A constrained optimization problem The trained matrix The lung cancer network Unbiased diffusion process

## Our first approximation

- For each primary in data set, use raw numbers to fill out rows
- Normalize each of those rows by dividing by sum
- Fill out entries for the remaining empty rows with 'unbiased' values  $a_{ij} = 1/50$
- A<sub>0</sub> constructed this way is a stochastic transition matrix
- But  $\vec{v}_T(A_0 I) \neq 0$

ヘロン ヘアン ヘビン ヘビン

Finding a 'good'  $A_0$ 

A constrained optimization problem The trained matrix The lung cancer network Unbiased diffusion process

## Our first approximation

- For each primary in data set, use raw numbers to fill out rows
- Normalize each of those rows by dividing by sum
- Fill out entries for the remaining empty rows with 'unbiased' values  $a_{ij} = 1/50$
- A₀ constructed this way is a stochastic transition matrix
  But v
  <sub>T</sub>(A₀ − I) ≠ 0

ヘロン ヘアン ヘビン ヘビン

# Finding a 'good' $A_0$

A constrained optimization problem The trained matrix The lung cancer network Unbiased diffusion process

## Our first approximation

- For each primary in data set, use raw numbers to fill out rows
- Normalize each of those rows by dividing by sum
- Fill out entries for the remaining empty rows with 'unbiased' values  $a_{ij} = 1/50$
- A<sub>0</sub> constructed this way is a stochastic transition matrix
  But v
  <sub>T</sub>(A<sub>0</sub> − I) ≠ 0

Finding a 'good'  $A_0$ 

A constrained optimization problem The trained matrix The lung cancer network Unbiased diffusion process

## Our first approximation

- For each primary in data set, use raw numbers to fill out rows
- Normalize each of those rows by dividing by sum
- Fill out entries for the remaining empty rows with 'unbiased' values  $a_{ij} = 1/50$
- A<sub>0</sub> constructed this way is a stochastic transition matrix
- But  $\vec{v}_T(A_0 I) \neq 0$

ヘロン ヘアン ヘビン ヘビン

The trained matrix The lung cancer network Unbiased diffusion proces

A constrained optimization problem

## Dynamics using $A_0$



Conclusions

Dynamics using  $A_0$ 

A constrained optimization problem



P.K. Newton Metastatic progression on networks

A constrained optimization problem The trained matrix The lung cancer network Unbiased diffusion process

## Dynamics using $A_0$



P.K. Newton Metastatic progression on networks

A constrained optimization problem The trained matrix The lung cancer network Unbiased diffusion process

## Dynamics using $A_0$

### $k = \infty$ : Does not converge to the correct steady-state



P.K. Newton Metastatic progression on networks

A constrained optimization problem The trained matrix The lung cancer network Unbiased diffusion process

Iterating  $A_j$ , j = 0, 1, 2, ...

- Calculate the residual  $\vec{r}_j$  at step j
- Pick column of A<sub>j</sub> corresponding to position of max entry of r<sub>j</sub>
- Pick column of A<sub>j</sub> corresponding to position of min entry of  $\vec{r}_j$
- Pick a row of A<sub>i</sub> at random
- Decrease entry of A<sub>j</sub> in step 2 by δ, increase entry of A<sub>j</sub> in step 3 by δ, where δ scales with ||r<sub>j</sub>||<sup>2</sup>. The new matrix is A<sub>j+1</sub>.
- Stop if  $\|\vec{r}_{j+1}\|^2 < \epsilon$ , otherwise go to step 2 and repeat.

A constrained optimization problem The trained matrix The lung cancer network Unbiased diffusion process

Iterating  $A_j$ , j = 0, 1, 2, ...

- Calculate the residual  $\vec{r_i}$  at step j
- Pick column of A<sub>j</sub> corresponding to position of max entry of r<sub>j</sub>
- Pick column of A<sub>j</sub> corresponding to position of min entry of  $\vec{r}_j$
- Pick a row of A<sub>i</sub> at random
- Decrease entry of A<sub>j</sub> in step 2 by δ, increase entry of A<sub>j</sub> in step 3 by δ, where δ scales with ||r<sub>j</sub>||<sup>2</sup>. The new matrix is A<sub>j+1</sub>.
- Stop if  $\|\vec{r}_{j+1}\|^2 < \epsilon$ , otherwise go to step 2 and repeat.

A constrained optimization problem The trained matrix The lung cancer network Unbiased diffusion process

Iterating  $A_j$ , j = 0, 1, 2, ...

- Calculate the residual  $\vec{r}_j$  at step j
- 2 Pick column of  $A_j$  corresponding to position of max entry of  $\vec{r}_j$
- Pick column of  $A_j$  corresponding to position of min entry of  $\vec{r}_j$
- Pick a row of A<sub>j</sub> at random
- Decrease entry of A<sub>j</sub> in step 2 by δ, increase entry of A<sub>j</sub> in step 3 by δ, where δ scales with ||r<sub>j</sub>||<sup>2</sup>. The new matrix is A<sub>j+1</sub>.
- Stop if  $\|\vec{r}_{j+1}\|^2 < \epsilon$ , otherwise go to step 2 and repeat.

A constrained optimization problem The trained matrix The lung cancer network Unbiased diffusion process

Iterating  $A_j$ , j = 0, 1, 2, ...

- Calculate the residual  $\vec{r}_j$  at step j
- 2 Pick column of  $A_j$  corresponding to position of max entry of  $\vec{r}_j$
- Pick column of  $A_j$  corresponding to position of min entry of  $\vec{r}_j$
- Pick a row of A<sub>i</sub> at random
- Decrease entry of A<sub>j</sub> in step 2 by δ, increase entry of A<sub>j</sub> in step 3 by δ, where δ scales with ||r<sub>j</sub>||<sup>2</sup>. The new matrix is A<sub>j+1</sub>.
- Stop if  $\|\vec{r}_{j+1}\|^2 < \epsilon$ , otherwise go to step 2 and repeat.

A constrained optimization problem The trained matrix The lung cancer network Unbiased diffusion process

Iterating  $A_j$ , j = 0, 1, 2, ...

- Calculate the residual  $\vec{r}_j$  at step j
- 2 Pick column of  $A_j$  corresponding to position of max entry of  $\vec{r}_j$
- Pick column of  $A_j$  corresponding to position of min entry of  $\vec{r}_j$
- Pick a row of A<sub>j</sub> at random
- Decrease entry of A<sub>j</sub> in step 2 by δ, increase entry of A<sub>j</sub> in step 3 by δ, where δ scales with ||r<sub>j</sub>||<sup>2</sup>. The new matrix is A<sub>j+1</sub>.
- 3 Stop if  $\|\vec{r}_{j+1}\|^2 < \epsilon$ , otherwise go to step 2 and repeat.

A constrained optimization problem The trained matrix The lung cancer network Unbiased diffusion process

Iterating  $A_j$ , j = 0, 1, 2, ...

- Calculate the residual  $\vec{r_j}$  at step j
- 2 Pick column of  $A_j$  corresponding to position of max entry of  $\vec{r}_j$
- Pick column of  $A_j$  corresponding to position of min entry of  $\vec{r}_j$
- Pick a row of A<sub>i</sub> at random
- Obcrease entry of A<sub>j</sub> in step 2 by δ, increase entry of A<sub>j</sub> in step 3 by δ, where δ scales with ||r<sub>j</sub>||<sup>2</sup>. The new matrix is A<sub>j+1</sub>.
- Stop if  $\|\vec{r}_{j+1}\|^2 < \epsilon$ , otherwise go to step 2 and repeat.

A constrained optimization problem The trained matrix The lung cancer network Unbiased diffusion process

### Convergence to the fully 'trained' matrix



P.K. Newton Metastatic progression on networks

・ロト ・四ト ・ヨト ・ヨト

æ

A constrained optimization problem The trained matrix The lung cancer network Unbiased diffusion process

## k = 0: State-vector dynamics using trained lung cancer matrix



프 🕨 🗉 프

A constrained optimization problem The trained matrix The lung cancer network Unbiased diffusion process

## k = 2: State-vector dynamics using trained lung cancer matrix



'문▶ '문

A constrained optimization problem The trained matrix The lung cancer network Unbiased diffusion process

## k = 10: State-vector dynamics using trained lung cancer matrix



프 🕨 🗉 프

A constrained optimization problem The trained matrix The lung cancer network Unbiased diffusion process

#### $k = \infty$ : State-vector dynamics using trained lung cancer matrix



프 🕨 🗉 프

A constrained optimization problem The trained matrix The lung cancer network Unbiased diffusion process

## Eigenvalue distribution of lung cancer matrix



P.K. Newton Metastatic progression on networks
A constrained optimization problem The trained matrix The lung cancer network Unbiased diffusion process

## The lung cancer network



P.K. Newton Metastatic progression on networks

DQC

A constrained optimization problen The trained matrix **The lung cancer network** Unbiased diffusion process

## Summary of network structure

- Total of 913 edges
- Lung node has 21 outgoing edges
- Lung node has 49 incoming edges



< ∃→

A constrained optimization problen The trained matrix **The lung cancer network** Unbiased diffusion process

## Importance of secondary connections



A constrained optimization problem The trained matrix **The lung cancer network** Unbiased diffusion process

## Importance of secondary connections



э

The lung cancer network

## Importance of secondary connections

## k = 2: 6 'Second order connections' - 'mets from mets'



< < >> < </>

< ∃→

э

P.K. Newton

A constrained optimization problem The trained matrix **The lung cancer network** Unbiased diffusion process

## Importance of secondary connections



프 🕨 🗉 프

A constrained optimization problem The trained matrix **The lung cancer network** Unbiased diffusion process

## Importance of secondary connections



프 🕨 🗉 프

A constrained optimization problem The trained matrix The lung cancer network Unbiased diffusion process

# 'Second order' cancers (from primary lung)

## Mets from mets

- bladder
- prostate
- skeletal muscle
- skin
- uterus
- vagina

ヘロト ヘ戸ト ヘヨト ヘヨト

э

A constrained optimization problen The trained matrix The lung cancer network Unbiased diffusion process

#### The most heavily weighted incoming connections



ヘロア 人間 アメヨア 人口 ア

э

Cut-off: 0.4

A constrained optimization problen The trained matrix The lung cancer network Unbiased diffusion process

Strongest connections all go to the (24) Lymph nodes (reg) and (33) Pleura to (1) Adrenal.



A constrained optimization problem The trained matrix The lung cancer network Unbiased diffusion process

# Cut-off: 0.25

Strongest connections to (24) Lymph nodes (reg), (25) Lymph nodes (dist), (23) Lung, and (46) Tonsil to (41) Spleen.



P.K. Newton Metastatic progression on networks

# Cut-off: 0.1

A constrained optimization probler The trained matrix **The lung cancer network** Unbiased diffusion process

Connections to (24) Lymph nodes (reg), (25) Lymph nodes (dist), (23) Lung, (22) Liver, new connections to (1) Adrenal, (6) Bone, (7) Brain, and (17) Heart.



A constrained optimization problem The trained matrix The lung cancer network Unbiased diffusion process

## Question: Would a 'pure diffusion' process work?

 Suppose we replace the heterogeneous edge weightings with 'unbiased' weighting where edge weights are distributed equally across all outgoing edges at each node.

ヘロン ヘアン ヘビン ヘビン

э

A constrained optimization problem The trained matrix The lung cancer network Unbiased diffusion process

## Question: Would a 'pure diffusion' process work?

 Suppose we replace the heterogeneous edge weightings with 'unbiased' weighting where edge weights are distributed equally across all outgoing edges at each node.

ヘロト 人間 ト ヘヨト ヘヨト

A constrained optimization problem The trained matrix The lung cancer network Unbiased diffusion process

## k = 0: State-vector dynamics using unbiased edge weightings



≣⇒ ≣

A constrained optimization problem The trained matrix The lung cancer network Unbiased diffusion process

## k = 2: State-vector dynamics using unbiased edge weightings



'문▶ '문

A constrained optimization problem The trained matrix The lung cancer network Unbiased diffusion process

## k = 10: State-vector dynamics using unbiased edge weightings



'문▶ '문

A constrained optimization problem The trained matrix The lung cancer network Unbiased diffusion process

#### $k = \infty$ : Does not converge to correct steady-state



æ

< ∃→

Individual trajectories Mean first-passage times Singular value decomposition

# One 'Monte Carlo' trajectory from the lung



How many steps (on average) does it take to go from lung
 → node *i* ?

Individual trajectories Mean first-passage times Singular value decomposition

## Mean first-passage time matrix

$$Z = (I - P + W)^{-1}$$

- $I : n \times n$  identity matrix
- P :  $n \times n$  transition matrix
- W : rows are steady-state

$$m_{ij} = \frac{Z_{jj} - Z_{ij}}{W_j}$$

Z matrix also gives variances

・ロト ・ 理 ト ・ ヨ ト ・

Individual trajectories Mean first-passage times Singular value decomposition

Lymph Nodes (reg)         5.3295         4.86733           Lymph Nodes (dist)         7.8069         7.38658           Liver         9.7405         9.21283           Adrenal         9.9006         9.38006           Lung         12.8793         12.5152           Bone         18.3202         18.2009           Kidney         20.1983         19.9714           Pleura         21.9595         21.368           Pancreas         26.0553         25.4704           Spleen         34.7067         34.1273           Heart         36.6631         35.8982           Thyroid         40.4995         39.5196           Brain         40.9396         41.1525           Pericardium         48.652         46.7418           Peritoneum         51.0337         50.0885           Diaphragm         52.1855         50.7323           Large Intestine         68.9146         68.2363           Skin         79.334         77.3178           Gallbladder         104.491         102.993           Stomach         122.915         122.968           Omentum         156.996         155.52           Skeletal Muscle <td< th=""><th>Mean First Passage</th><th>Fime from Lung</th><th>Variance</th><th></th></td<>	Mean First Passage	Fime from Lung	Variance	
Lymph Nodes (dist)         7.8069         7.38658           Liver         9.7405         9.21283           Adrenal         9.9006         9.38006           Lung         12.8793         12.5152           Bone         18.3202         18.2009           Kidney         20.1983         19.9714           Pleura         21.9595         21.368           Pancreas         26.0553         25.4704           Spleen         34.7067         34.1273           Heart         36.6631         35.8982           Thyroid         40.4995         39.5196           Brain         40.9396         41.1525           Pericardium         48.652         46.7418           Pericardium         48.652         46.7418           Pericardium         68.9146         68.2363           Skin         79.334         77.3178           Gallbladder         104.491         102.993           Stomach         122.915         122.968           Omentum         156.996         155.52           Skeletal Muscle         308.253         308.538           Uterus         604.221         600.579           Bladder         614.423	Lymph Nodes (reg)	5.3295	4.86733	
Liver         9.7405         9.21283           Adrenal         9.9006         9.38006           Lung         12.8793         12.5152           Bone         18.3202         18.2009           Kidney         20.1983         19.9714           Pleura         21.9595         21.368           Pancreas         26.0553         25.4704           Spleen         34.7067         34.1273           Heart         36.6631         35.8982           Thyroid         40.4995         39.5196           Brain         40.3936         41.1525           Pericardium         48.652         46.7418           Peritoneum         51.0337         50.0885           Diaphragm         52.1855         50.7323           Large Intestine         68.9146         68.2363           Skin         79.334         77.3178           Gallbladder         104.491         102.993           Stomach         122.915         122.968           Omentum         156.996         155.52           Skeletal Muscle         308.253         308.538           Uterus         604.221         600.579           Bladder         614.423	Lymph Nodes (dist)	7.8069	7.38658	
Adrenal         9.9006         9.38006           Lung         12.8793         12.5152           Bone         18.3202         18.2009           Kidney         20.1983         19.9714           Pleura         21.9595         21.368           Pancreas         26.0553         25.4704           Spleen         34.7067         34.1273           Heart         36.6631         35.8982           Thyroid         40.4995         39.5196           Brain         40.3936         41.1525           Pericardium         48.652         46.7418           Peritoneum         51.0337         50.0885           Diaphragm         52.1855         50.7323           Large Intestine         68.9146         68.2363           Skin         79.334         77.3178           Gallbladder         104.491         102.993           Stomach         122.915         122.968           Omentum         156.996         155.52           Skeletal Muscle         308.253         308.538           Uterus         604.221         600.579           Bladder         619.438         628.354           Vagina         629.237	Liver	9.7405	9.21283	
Lung         12.8793         12.5152           Bone         18.3202         18.2009           Kidney         20.1983         19.9714           Pleura         21.9595         21.368           Pancreas         26.0553         25.4704           Spleen         34.7067         34.1273           Heart         36.6631         35.8982           Thyroid         40.4995         39.5196           Brain         40.9396         41.1525           Pericardium         48.652         46.7418           Pericardium         51.0337         50.0885           Diaphragm         52.1855         50.7323           Large Intestine         68.9146         68.2363           Skin         79.334         77.3178           Gallbladder         104.151         101.483           Small Intestine         104.491         102.993           Stomach         122.915         122.968           Omentum         156.996         155.52           Skeletal Muscle         308.538           Uterus         604.221         600.579           Bladder         619.438         628.354           Vagina         629.237         642.475	Adrenal	9.9006	9.38006	
Bone         18.3202         18.2009           Kidney         20.1983         19.9714           Pleura         21.9595         21.368           Pancreas         26.0553         25.4704           Spleen         34.7067         34.1273           Heart         36.6631         35.8982           Thyroid         40.4995         39.5196           Brain         40.9396         41.1525           Pericardium         48.652         46.7418           Peritoneum         51.0337         50.0885           Diaphragm         52.1855         50.7323           Large Intestine         68.9146         68.2363           Skin         79.334         77.3178           Gallbladder         104.491         102.993           Stomach         122.915         122.968           Omentum         156.996         155.52           Skeletal Muscle         308.538         Uterus           Oldez         604.221         600.579           Bladder         614.423         622.782           Prostate         619.438         628.354           Vagina         629.237         642.475	Lung	12.8793	12.5152	
Kidney         20.1983         19.9714           Pleura         21.9595         21.368           Pancreas         26.0553         25.4704           Spleen         34.7067         34.1273           Heart         36.6631         35.8982           Thyroid         40.4995         39.5196           Brain         40.9396         41.1525           Pericardium         48.652         46.7418           Peritoneum         51.0337         50.0885           Diaphragm         52.1855         50.7323           Large Intestine         68.9146         68.2363           Skin         79.334         77.3178           Gallbladder         104.491         102.993           Stomach         122.915         122.968           Omentum         156.996         155.52           Skeletal Muscle         308.253         308.538           Uterus         604.221         600.579           Bladder         614.423         622.782           Prostate         619.438         628.54           Vagina         629.237         642.475	Bone	18.3202	18.2009	
Pleura         21,9595         21,368           Pancreas         26,0553         25,4704           Spleen         34,7067         34,1273           Heart         36,6631         35,8982           Thyroid         40,4995         39,5196           Brain         40,9396         41,1525           Pericardium         48,652         46,7418           Peritoneum         51,0337         50,0885           Diaphragm         52,1855         50,7323           Large Intestine         68,9146         68,2363           Skin         79,334         77,3178           Gallbladder         104,151         101,483           Small Intestine         104,491         102,993           Stomach         122,915         122,968           Omentum         156,996         155,52           Skeletal Muscle         308,253         308,538           Uterus         604,221         600,579           Bladder         619,438         622,782           Prostate         619,237         642,475	Kidney	20.1983	19.9714	
Pancreas         26.0553         25.4704           Spleen         34.7067         34.1273           Heart         36.6631         35.8982           Thyroid         40.4995         39.5196           Brain         40.9396         41.1525           Pericardium         48.652         46.7418           Peritoneum         51.0337         50.0885           Diaphragm         52.1855         50.7323           Large Intestine         68.9146         68.2363           Skin         79.334         77.3178           Gallbladder         104.491         102.993           Stomach         122.915         122.968           Omentum         156.996         155.52           Skeletal Muscle         308.253         308.538           Uterus         604.221         600.579           Bladder         619.438         622.782           Prostate         619.438         628.354           Vagina         629.237         642.475	Pleura	21.9595	21.368	
Spleen         34.7067         34.1273           Heart         36.6631         35.8982           Thyroid         40.4995         39.5196           Brain         40.9396         41.1525           Pericardium         48.652         46.7418           Peritoneum         51.0337         50.0885           Diaphragm         52.1855         50.7323           Large Intestine         68.9146         68.2363           Skin         79.334         77.3178           Gallbladder         104.491         102.993           Stomach         122.915         122.968           Omentum         156.996         155.52           Skeletal Muscle         308.253         308.538           Uterus         604.221         600.579           Bladder         614.423         622.782           Prostate         619.438         628.354           Vagina         629.237         642.475	Pancreas	26.0553	25.4704	
Heart         36.6631         35.8982           Thyroid         40.4995         39.5196           Brain         40.9396         41.1525           Pericardium         48.652         46.7418           Peritoneum         51.0337         50.0885           Diaphragm         52.1855         50.7323           Large Intestine         68.9146         68.2363           Skin         79.334         77.3178           Gallbladder         104.151         101.483           Small Intestine         104.491         102.993           Stomach         122.915         122.968           Omentum         156.996         155.52           Skeletal Muscle         308.253         308.538           Uterus         604.221         600.579           Bladder         619.438         628.354           Vagina         629.237         642.475	Spleen	34.7067	34.1273	
Thyroid         40.4995         39.5196           Brain         40.9396         41.1525           Pericardium         48.652         46.7418           Peritoneum         51.0337         50.0885           Diaphragm         52.1855         50.7323           Large Intestine         68.9146         68.2363           Skin         79.334         77.3178           Gallbladder         104.491         102.993           Stomach         122.915         122.968           Omentum         156.996         155.52           Skeletal Muscle         308.253         308.538           Uterus         604.221         600.579           Bladder         614.423         622.782           Prostate         619.438         628.354           Vagina         629.237         642.475	Heart	36.6631	35.8982	
Brain         40.9396         41.1525           Pericardium         48.652         46.7418           Peritoneum         51.0337         50.0885           Diaphragm         52.1855         50.7323           Large Intestine         68.9146         68.2363           Skin         79.334         77.3178           Gallbladder         104.151         101.483           Small Intestine         104.491         102.993           Stomach         122.915         122.968           Omentum         156.996         155.52           Skeletal Muscle         308.253         308.538           Uterus         604.221         600.579           Bladder         614.423         622.782           Prostate         619.438         628.354           Vagina         629.237         642.475	Thyroid	40.4995	39.5196	
Pericardium         48.652         46.7418           Peritoneum         51.0337         50.0885           Diaphragm         52.1855         50.7323           Large Intestine         68.9146         68.2363           Skin         79.334         77.3178           Gallbladder         104.151         101.483           Small Intestine         104.491         102.993           Stomach         122.915         122.968           Omentum         156.996         155.52           Skeletal Muscle         308.253         308.538           Uterus         604.221         600.579           Bladder         619.438         622.782           Prostate         619.237         642.475	Brain	40.9396	41.1525	
Pertioneum         51.0337         50.0885           Diaphragm         52.1855         50.7323           Large Intestine         68.9146         68.2363           Skin         79.334         77.3178           Gallbladder         104.151         101.483           Small Intestine         104.491         102.993           Stomach         122.915         122.968           Omentum         156.996         155.52           Skeletal Muscle         308.253         308.538           Uterus         604.221         600.579           Bladder         619.438         622.782           Vagina         629.237         642.475	Pericardium	48.652	46.7418	
Diaphragm         52.1855         50.7323           Large Intestine         68.9146         68.2363           Skin         79.334         77.3178           Gallbladder         104.151         101.483           Small Intestine         104.491         102.993           Stomach         122.915         122.968           Omentum         156.996         155.52           Skeletal Muscle         308.253         308.538           Uterus         604.221         600.579           Bladder         614.423         622.782           Prostate         619.438         628.354           Vagina         629.237         642.475	Peritoneum	51.0337	50.0885	
Large Intestine         68.9146         68.2363           Skin         79.334         77.3178           Gallbladder         104.151         101.483           Small Intestine         104.491         102.993           Stomach         122.915         122.968           Omentum         156.996         155.52           Skeletal Muscle         308.253         308.538           Uterus         604.221         600.579           Bladder         619.438         622.782           Yagina         629.237         642.475	Diaphragm	52.1855	50.7323	
Skin         79.334         77.3178           Gallbladder         104.151         101.483           Small Intestine         104.491         102.993           Stomach         122.915         122.968           Omentum         156.996         155.52           Skeletal Muscle         308.253         308.538           Uterus         604.221         600.579           Bladder         614.423         622.782           Vagina         629.237         642.475	Large Intestine	68.9146	68.2363	
Gallbladder         104.151         101.483           Small Intestine         104.491         102.993           Stomach         122.915         122.968           Omentum         156.996         155.52           Skeletal Muscle         308.253         308.538           Uterus         604.221         600.579           Bladder         614.423         622.782           Prostate         619.438         628.354           Vagina         629.237         642.475	Skin	79.334	77.3178	
Small Intestine         104.491         102.993           Stomach         122.915         122.968           Omentum         156.996         155.52           Skeletal Muscle         308.253         308.538           Uterus         604.221         600.579           Bladder         614.423         622.782           Prostate         619.438         628.354           Vagina         629.237         642.475	Gallbladder	104.151	101.483	
Stomach         122.915         122.968           Omentum         156.996         155.52           Skeletal Muscle         308.253         308.538           Uterus         604.221         600.579           Bladder         619.438         622.782           Prostate         619.438         628.354           Vagina         629.237         642.475	Small Intestine	104.491	102.993	
Omentum         156.996         155.52           Skeletal Muscle         308.253         308.538           Uterus         604.221         600.579           Bladder         614.423         622.782           Prostate         619.438         628.354           Vagina         629.237         642.475	Stomach	122.915	122.968	
Skeletal Muscle         308.253         308.538           Uterus         604.221         600.579           Bladder         614.423         622.782           Prostate         619.438         628.354           Vagina         629.237         642.475	Omentum	156.996	155.52	
Uterus         604.221         600.579           Bladder         614.423         622.782           Prostate         619.438         628.354           Vagina         629.237         642.475	Skeletal Muscle	308.253	308.538	
Bladder         614.423         622.782           Prostate         619.438         628.354           Vagina         629.237         642.475	Uterus	604.221	600.579	
Prostate 619.438 628.354 Vagina 629.237 642.475	Bladder	614.423	622.782	
Vagina 629.237 642.475	Prostate	619.438	628.354	
	Vagina	629.237	642.475	

P.K. Newton Metastatic progression on networks

Mean first-passage times

## Mean first-passage times



P.K. Newton Metastatic progression on networks

Individual trajectories Mean first-passage times Singular value decomposition

## The mean first-passage time trajectory



Individual trajectories Mean first-passage times Singular value decomposition

### Mean first-passage time ordering

Lung  $\rightarrow$  Lymph nodes (reg) (1 time unit) Lung  $\rightarrow$  Lymph nodes (dist) (1.46 time units) Lung  $\rightarrow$  Liver (1.83 time units) Lung  $\rightarrow$  Adrenal (1.86 time units) Lung  $\rightarrow$  Lung (2.42 time units) Lung  $\rightarrow$  Bone (3.44 time units) Lung  $\rightarrow$  Kidney (3.79 time units) Lung  $\rightarrow$  Pleura (4.12 time units) Lung  $\rightarrow$  Pancreas (4.89 time units)

P.K. Newton Metastatic progression on networks

・ロ・ ・ 同・ ・ ヨ・ ・ ヨ・

Individual trajectories Mean first-passage times Singular value decomposition

#### Mean first-passage time ordering

Lung  $\rightarrow$  Lymph nodes (reg) (1 time unit) Lung  $\rightarrow$  Lymph nodes (dist) (1.46 time units) Lung  $\rightarrow$  Liver (1.83 time units) Lung  $\rightarrow$  Adrenal (1.86 time units) Lung  $\rightarrow$  Lung (2.42 time units) Lung  $\rightarrow$  Bone (3.44 time units) Lung  $\rightarrow$  Kidney (3.79 time units) Lung  $\rightarrow$  Pleura (4.12 time units) Lung  $\rightarrow$  Pancreas (4.89 time units)

・ロ・ ・ 同・ ・ ヨ・ ・ ヨ・

Individual trajectories Mean first-passage times Singular value decomposition

## Mean first-passage time ordering

Lung  $\rightarrow$  Lymph nodes (reg) (1 time unit)

Lung  $\rightarrow$  Lymph nodes (dist) (1.46 time units)

Lung  $\rightarrow$  Liver (1.83 time units)

Lung  $\rightarrow$  Adrenal (1.86 time units)

Lung ightarrow Lung (2.42 time units)

Lung  $\rightarrow$  **Bone** (3.44 time units)

Lung  $\rightarrow$  Kidney (3.79 time units)

Lung  $\rightarrow$  **Pleura** (4.12 time units)

Lung  $\rightarrow$  **Pancreas** (4.89 time units)

・ロト ・ 理 ト ・ ヨ ト ・

Individual trajectories Mean first-passage times Singular value decomposition

## Mean first-passage time ordering

- Lung  $\rightarrow$  Lymph nodes (reg) (1 time unit)
- Lung  $\rightarrow$  Lymph nodes (dist) (1.46 time units)
- Lung  $\rightarrow$  Liver (1.83 time units)
- Lung  $\rightarrow$  Adrenal (1.86 time units)
- Lung  $\rightarrow$  Lung (2.42 time units)
- Lung  $\rightarrow$  Bone (3.44 time units)
- Lung  $\rightarrow$  Kidney (3.79 time units)
- Lung  $\rightarrow$  Pleura (4.12 time units)
- Lung  $\rightarrow$  Pancreas (4.89 time units)

・ロ・ ・ 同・ ・ ヨ・ ・ ヨ・

Individual trajectories Mean first-passage times Singular value decomposition

## Mean first-passage time ordering

- Lung  $\rightarrow$  Lymph nodes (reg) (1 time unit)
- Lung  $\rightarrow$  Lymph nodes (dist) (1.46 time units)
- Lung  $\rightarrow$  Liver (1.83 time units)
- Lung  $\rightarrow$  Adrenal (1.86 time units)
- Lung  $\rightarrow$  Lung (2.42 time units)
- Lung  $\rightarrow$  **Bone** (3.44 time units)
- Lung  $\rightarrow$  Kidney (3.79 time units)
- Lung  $\rightarrow$  Pleura (4.12 time units)
- Lung  $\rightarrow$  Pancreas (4.89 time units)

・ロ・ ・ 同・ ・ ヨ・ ・ ヨ・

Individual trajectories Mean first-passage times Singular value decomposition

## Mean first-passage time ordering

- Lung  $\rightarrow$  Lymph nodes (reg) (1 time unit)
- Lung  $\rightarrow$  Lymph nodes (dist) (1.46 time units)
- Lung  $\rightarrow$  Liver (1.83 time units)
- Lung  $\rightarrow$  Adrenal (1.86 time units)
- Lung  $\rightarrow$  Lung (2.42 time units)
- Lung  $\rightarrow$  Bone (3.44 time units)
- Lung  $\rightarrow$  Kidney (3.79 time units)
- Lung  $\rightarrow$  Pleura (4.12 time units)
- Lung  $\rightarrow$  Pancreas (4.89 time units)

・ロ・ ・ 同・ ・ ヨ・ ・ ヨ・

Individual trajectories Mean first-passage times Singular value decomposition

## Mean first-passage time ordering

- Lung  $\rightarrow$  Lymph nodes (reg) (1 time unit)
- Lung  $\rightarrow$  Lymph nodes (dist) (1.46 time units)
- Lung  $\rightarrow$  Liver (1.83 time units)
- Lung  $\rightarrow$  Adrenal (1.86 time units)
- Lung  $\rightarrow$  Lung (2.42 time units)
- Lung  $\rightarrow$  Bone (3.44 time units)
- Lung  $\rightarrow$  Kidney (3.79 time units)

Lung  $\rightarrow$  Pleura (4.12 time units)

Lung  $\rightarrow$  **Pancreas** (4.89 time units)

ヘロン 人間 とくほ とくほ とう

Individual trajectories Mean first-passage times Singular value decomposition

## Mean first-passage time ordering

- Lung  $\rightarrow$  Lymph nodes (reg) (1 time unit)
- Lung  $\rightarrow$  Lymph nodes (dist) (1.46 time units)
- Lung  $\rightarrow$  Liver (1.83 time units)
- Lung  $\rightarrow$  Adrenal (1.86 time units)
- Lung  $\rightarrow$  Lung (2.42 time units)
- Lung  $\rightarrow$  Bone (3.44 time units)
- Lung  $\rightarrow$  Kidney (3.79 time units)
- Lung  $\rightarrow$  Pleura (4.12 time units)

Lung  $\rightarrow$  **Pancreas** (4.89 time units)

ヘロン 人間 とくほ とくほ とう

Individual trajectories Mean first-passage times Singular value decomposition

## Mean first-passage time ordering

- Lung  $\rightarrow$  Lymph nodes (reg) (1 time unit)
- Lung  $\rightarrow$  Lymph nodes (dist) (1.46 time units)
- Lung  $\rightarrow$  Liver (1.83 time units)
- Lung  $\rightarrow$  Adrenal (1.86 time units)
- Lung  $\rightarrow$  Lung (2.42 time units)
- Lung  $\rightarrow$  Bone (3.44 time units)
- Lung  $\rightarrow$  Kidney (3.79 time units)
- Lung  $\rightarrow$  Pleura (4.12 time units)
- Lung  $\rightarrow$  Pancreas (4.89 time units)

ヘロト 人間 ト ヘヨト ヘヨト

Individual trajectories Mean first-passage times Singular value decomposition

#### Mean first-passage times are Gaussian distributed rv's



P.K. Newton Metastatic progression on networks

Individual trajectories Mean first-passage times Singular value decomposition

## Singular value distribution of lung cancer matrix



Eigenvalues of the 'covariance' matrix A<sup>T</sup>A

P.K. Newton Metastatic progression on networks

# Conclusions

## Main points

- Metastatic progression can be thought of as a 'biased' random walk process on a network of potential metastatic sites.
- Pure diffusion process (unbiased random walk) is not a good model.
- Model identifies 21 'first-order' sites, and 6 'second-order' sites ('mets from mets')
- Model flags 9 sites (out of the 50 total number) with very short mean first-passage times.

イロト イポト イヨト イヨト

# Conclusions

## Main points

- Metastatic progression can be thought of as a 'biased' random walk process on a network of potential metastatic sites.
- Pure diffusion process (unbiased random walk) is not a good model.
- Model identifies 21 'first-order' sites, and 6 'second-order' sites ('mets from mets')
- Model flags 9 sites (out of the 50 total number) with very short mean first-passage times.

イロト イポト イヨト イヨト
# Conclusions

#### Main points

- Metastatic progression can be thought of as a 'biased' random walk process on a network of potential metastatic sites.
- Pure diffusion process (unbiased random walk) is not a good model.
- Model identifies 21 'first-order' sites, and 6 'second-order' sites ('mets from mets')
- Model flags 9 sites (out of the 50 total number) with very short mean first-passage times.

# Conclusions

#### Main points

- Metastatic progression can be thought of as a 'biased' random walk process on a network of potential metastatic sites.
- Pure diffusion process (unbiased random walk) is not a good model.
- Model identifies 21 'first-order' sites, and 6 'second-order' sites ('mets from mets')
- Model flags 9 sites (out of the 50 total number) with very short mean first-passage times.

# Conclusions

#### Secondary points

- Complex web of connections are important, not just outgoing ones from lung.
- Model supports the idea that metastatic development is the result of a complex and intricate pattern of cross-talk and communication among a large collection of potential nodes.
- Next: Comparisons of different cancer networks (lung, liver, breast, colon, prostate, ovarian)
- Individual patient histories and Bayesian updating

# Conclusions

#### Secondary points

- Complex web of connections are important, not just outgoing ones from lung.
- Model supports the idea that metastatic development is the result of a complex and intricate pattern of cross-talk and communication among a large collection of potential nodes.
- Next: Comparisons of different cancer networks (lung, liver, breast, colon, prostate, ovarian)
- Individual patient histories and Bayesian updating

# Conclusions

#### Secondary points

- Complex web of connections are important, not just outgoing ones from lung.
- Model supports the idea that metastatic development is the result of a complex and intricate pattern of cross-talk and communication among a large collection of potential nodes.
- Next: Comparisons of different cancer networks (lung, liver, breast, colon, prostate, ovarian)

Individual patient histories and Bayesian updating

# Conclusions

#### Secondary points

- Complex web of connections are important, not just outgoing ones from lung.
- Model supports the idea that metastatic development is the result of a complex and intricate pattern of cross-talk and communication among a large collection of potential nodes.
- Next: Comparisons of different cancer networks (lung, liver, breast, colon, prostate, ovarian)
- Individual patient histories and Bayesian updating

### References

- P.K. Newton, J. Mason, P. Kuhn, K. Bethel, J. Nieva, L. Bazhenova, Metastatic progression via biased random walks on a cancer network, USC preprint (2011).
- G. DiSibio, S.W. French [2008], Metastatic patterns of cancers: Results from a large autopsy study, *Arch Pathol Lab Med*, **Vol. 132**, June.
- KI Goh, ME Cusick, D Valle, B Childs, M Vidal, AL Barabasi [2007], The human disease network, *Proc. Nat'l Acad. Sci.* **104**, 8685-8690.
- J. Balthrop, S. Forrest, M.E.J. Newman [2004], Technological networks and the spread of computer viruses, *Science*, **304**, 5670, 527–529.
- NCI/NIH PS-OC: 'The Physics & Mathematics of Cancer Metastasis', 2010-2015.

・ロット (雪) ( ) ( ) ( ) ( )

### References

- P.K. Newton, J. Mason, P. Kuhn, K. Bethel, J. Nieva, L. Bazhenova, Metastatic progression via biased random walks on a cancer network, USC preprint (2011).
- G. DiSibio, S.W. French [2008], Metastatic patterns of cancers: Results from a large autopsy study, *Arch Pathol Lab Med*, Vol. 132, June.
- KI Goh, ME Cusick, D Valle, B Childs, M Vidal, AL Barabasi [2007], The human disease network, *Proc. Nat'l Acad. Sci.* **104**, 8685-8690.
- J. Balthrop, S. Forrest, M.E.J. Newman [2004], Technological networks and the spread of computer viruses, *Science*, **304**, 5670, 527–529.
- NCI/NIH PS-OC: 'The Physics & Mathematics of Cancer Metastasis', 2010-2015.

・ロ・ ・ 四・ ・ ヨ・ ・ ヨ・

### References

- P.K. Newton, J. Mason, P. Kuhn, K. Bethel, J. Nieva, L. Bazhenova, Metastatic progression via biased random walks on a cancer network, USC preprint (2011).
- G. DiSibio, S.W. French [2008], Metastatic patterns of cancers: Results from a large autopsy study, *Arch Pathol Lab Med*, Vol. 132, June.
- KI Goh, ME Cusick, D Valle, B Childs, M Vidal, AL Barabasi [2007], The human disease network, *Proc. Nat'l Acad. Sci.* **104**, 8685-8690.
- J. Balthrop, S. Forrest, M.E.J. Newman [2004], Technological networks and the spread of computer viruses, *Science*, **304**, 5670, 527–529.
- NCI/NIH PS-OC: 'The Physics & Mathematics of Cancer Metastasis', 2010-2015.

ヘロト 人間 ト ヘヨト ヘヨト

### References

- P.K. Newton, J. Mason, P. Kuhn, K. Bethel, J. Nieva, L. Bazhenova, Metastatic progression via biased random walks on a cancer network, USC preprint (2011).
- G. DiSibio, S.W. French [2008], Metastatic patterns of cancers: Results from a large autopsy study, *Arch Pathol Lab Med*, Vol. 132, June.
- KI Goh, ME Cusick, D Valle, B Childs, M Vidal, AL Barabasi [2007], The human disease network, *Proc. Nat'l Acad. Sci.* **104**, 8685-8690.
- J. Balthrop, S. Forrest, M.E.J. Newman [2004], Technological networks and the spread of computer viruses, *Science*, **304**, 5670, 527–529.
- NCI/NIH PS-OC: 'The Physics & Mathematics of Cancer Metastasis', 2010-2015.

ヘロア 人間 アメヨア 人口 ア