

ABC SMC for parameter estimation and model selection with applications in systems biology

Tina Toni

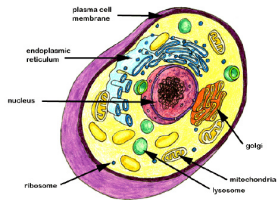
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ABC in London, 05/05/2011

Motivation

Complex biological systems

- Models often ODE or stochastic master equations
- High dimensional parameter space
- Time course, non-equidistant, missing data



Interested in

- Characterization of distributions over parameters rather than point estimates.
- What dynamic behaviour can reproduce data?
- Which models represent suitable hypothesis about the system?

Outline

Parameter estimation

- ABC basics
- ABC SMC
- Application: Modeling bacterial stress response

Model selection

- ABC SMC for model selection
- Application: Epo signaling pathway
- Application: Phosphorylation dynamics

Approximate Bayesian Computation basics

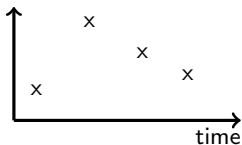
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- 2 Simulate a data set D^c from the model with θ^c .
- 3 If $\text{dist}(D, D^c) \leq \epsilon$, accept θ^c , otherwise reject.
- 4 Return to **1**.



Prior
 $P(\theta)$



Posterior
 $P(\theta|D)$



Approximate Bayesian Computation basics

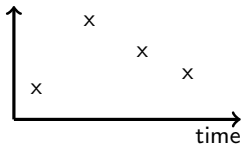
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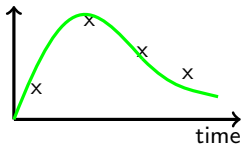
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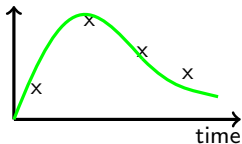
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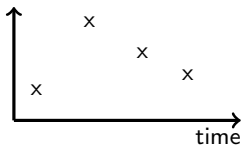
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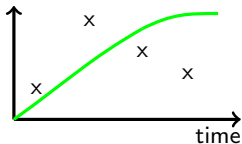
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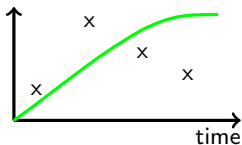
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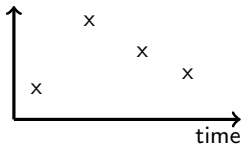
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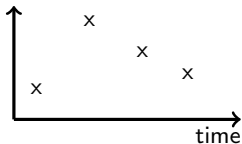
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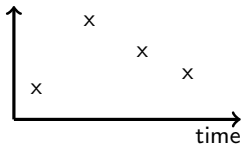


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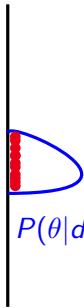


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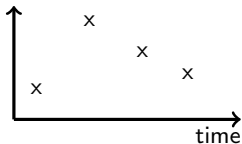


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ABC SMC (Sequential Monte Carlo)



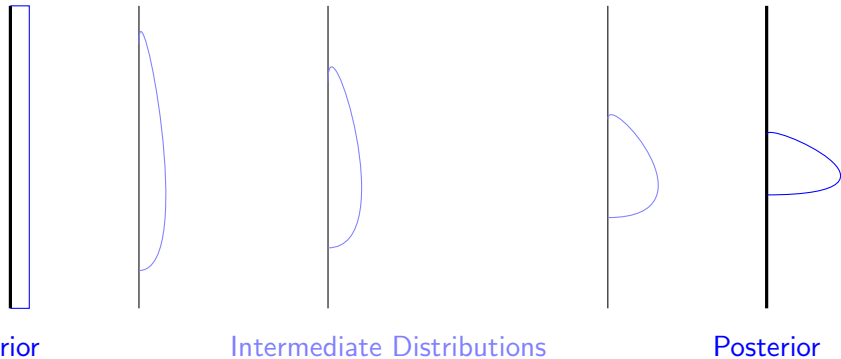
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Posterior

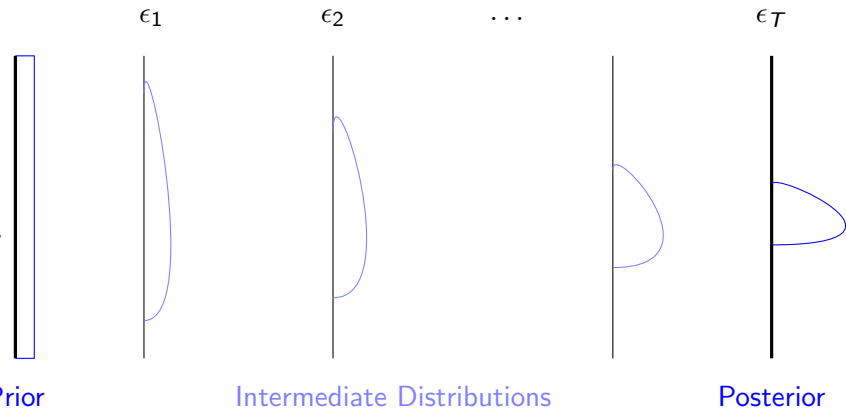
Gelman et al., 2007, PNAS)

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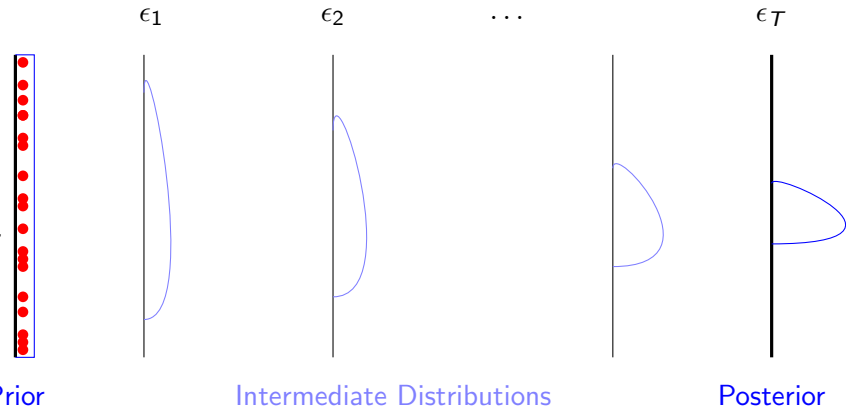
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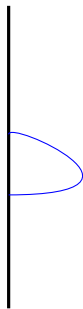
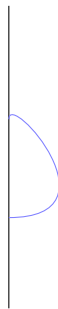
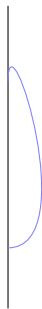
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ABC SMC (Sequential Monte Carlo)

Population 1

 ϵ_1 ϵ_2

...

 ϵ_T 

Prior

Intermediate Distributions

Posterior

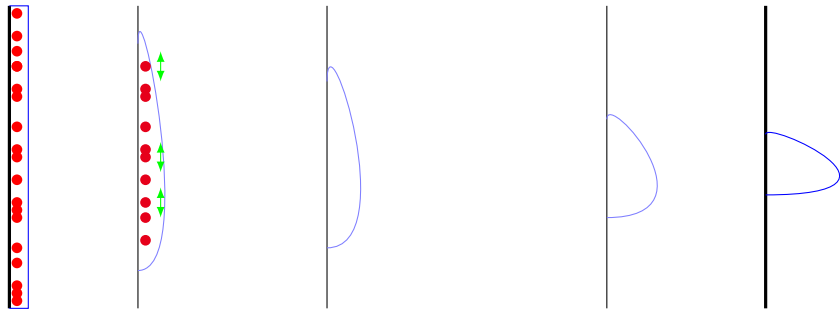
Precedings : doi:10.1038/npre.2011.5964.1 : Posted 13 May 2011
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Intermediate Distributions

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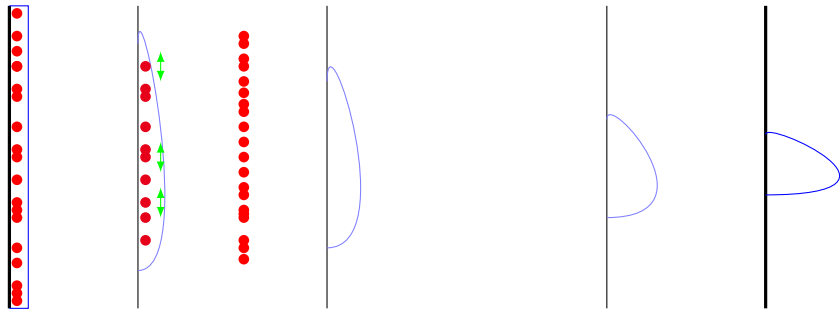
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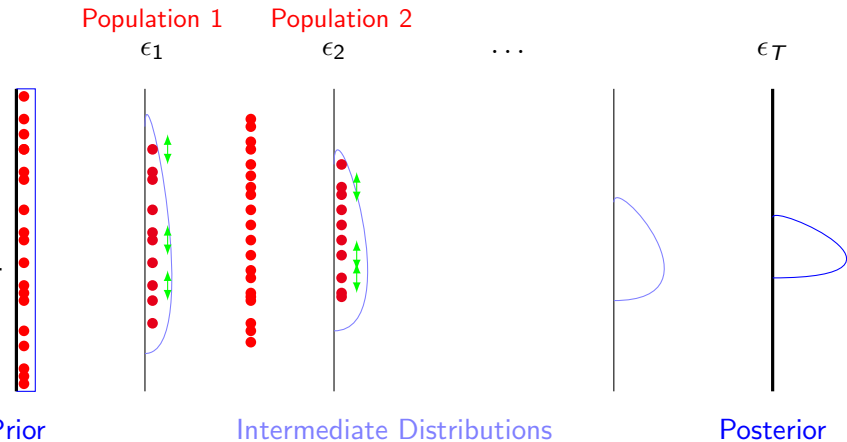
Prior

Intermediate Distributions

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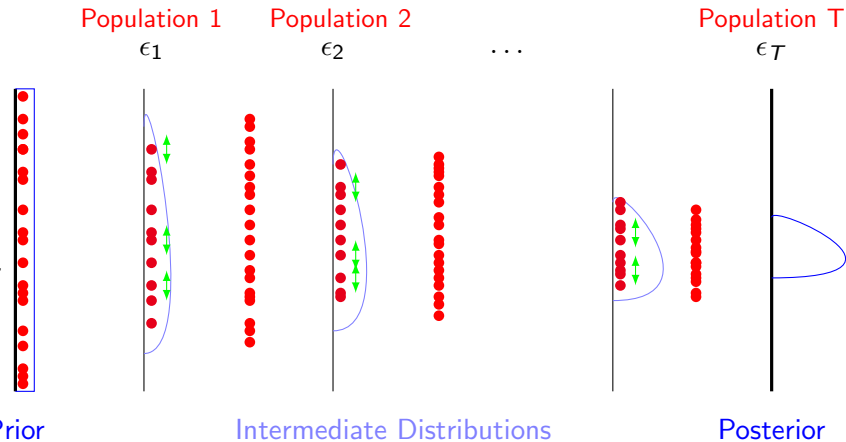
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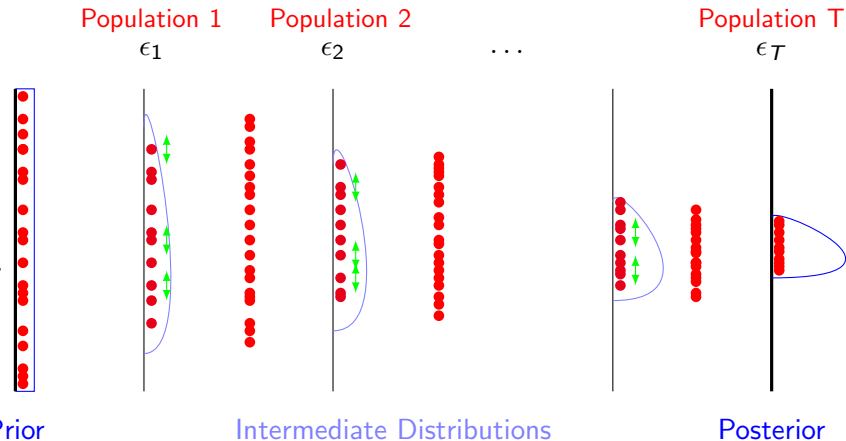
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ABC SMC (Sequential Monte Carlo)



(Gelman et al., 2007, PNAS)

ABC SMC (Sequential Monte Carlo)



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Weights

$$w_t(\theta_t) = \frac{\pi_t(\theta_t)}{\eta_t(\theta_t)}$$

$$\eta_t(\theta_t) = \mathbb{1}(\pi(\theta_t) > 0) \mathbb{1}(\text{dist} < \epsilon_t) \int \pi_{t-1}(\theta_{t-1}) K_t(\theta_t | \theta_{t-1}) d\theta_{t-1}$$

$$w_t^{(i)} = \frac{\pi(\theta_t^{(i)})}{\sum_{j=1}^N w_{t-1}^{(j)} K_t(\theta_t^{(i)} | \theta_{t-1}^{(j)})}$$

(Toni *et al.*, J. R. Soc. Interface, 2009)

Application: Modeling phage shock protein response in *Escherichia coli*

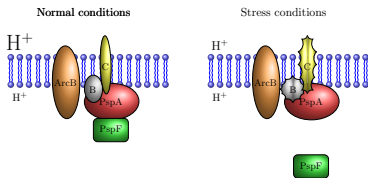
Signal

Phage damages the membrane of bacteria (we call this stress).

Response

- Reduced motility
- Anaerobic respiration
- Start membrane repair mechanisms etc.

Change shock protein response



Psp response

- 1 Stress
- 2 PspC changes conformation
- 3 PspB changes conformation
- 4 Complex PspA-PspF breaks
- 5 PspF is free to act as a transcription factor
- 6 Psp genes (A,B,C,D,E,F,G) \rightarrow proteins
- 7 Response

Data and Questions of interest

Data

- Details of molecular interactions.
- Kinetic parameters unknown.
- Few data available (qualitative end point data).

Data and Questions of interest

Data

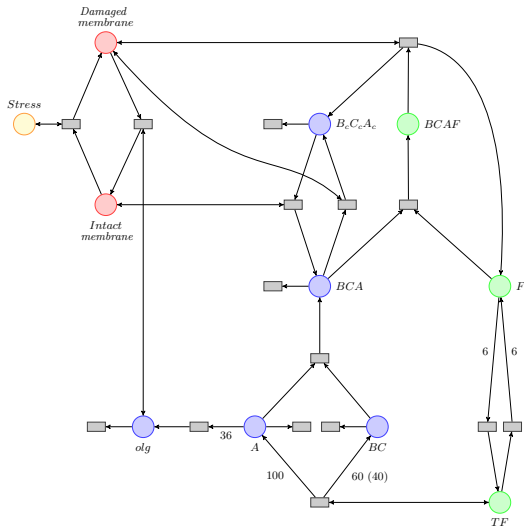
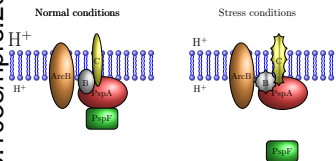
- Details of molecular interactions.
- Kinetic parameters unknown.
- Few data available (qualitative end point data).

Questions of interest

- 1 What dynamic behaviour is possible?
- 2 Can it be inferred from qualitative end-point data?
- 3 What happens when stress is removed?

Petri net model

Precedings : doi:10.1038/npre.2011.5964.1 : Posted 19 May 2011

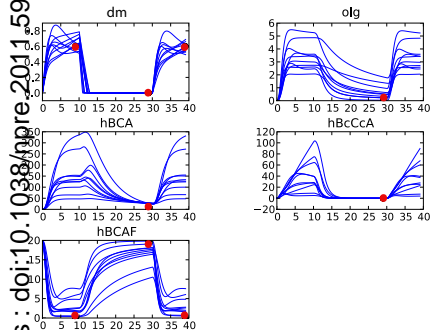


Toni, Jovanovic, Huvet, Buck, Stumpf, BMC Systems Biology, 2011 (in press)

Results: Possible qualitative behaviours

Stress induced: $t = [0, 10)$, $t = [30, 40)$.

Stress removed: $t = [10, 30)$



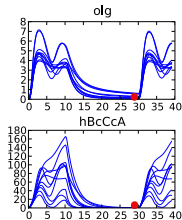
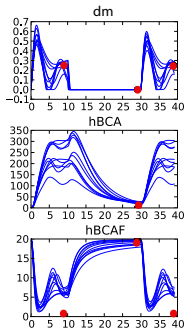
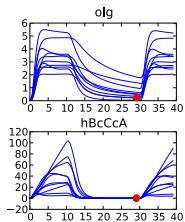
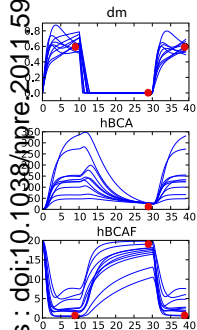
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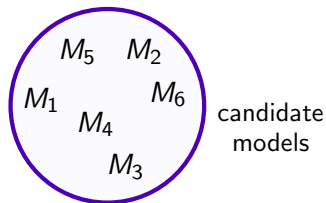
Stress removed: $t = [10, 30)$

Less severe stress \rightarrow oscillations.



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 Toni, Jovanovic, Huvet, Buck, Stumpf, BMC Systems Biology, 2011 (in press)

Bayesian model selection



Marginal posterior distribution of a model

$$P(M|D) \propto P(D|M)P(M)$$

$$P(M|D) \propto \int_{\theta} P(D|M, \theta)P(M)P(\theta|M)d\theta$$

Bayesian model selection

Fit to
the data



Number of
parameters

Model selection: $P(M|D) = ?$

1. Marginal likelihoods

- For each model separately estimate $P(D|M)$:

$$P(D|M) = \int_{\theta} P(D|\theta, M)P(\theta|M)d\theta$$

- Then

$$P(M|D) = \frac{P(D|M)P(M)}{\sum_{M'} P(D|M')P(M')}.$$

2. Joint space

- Include model M as an extra parameter:
 $(M, \theta^{(1)}, \dots, \theta^{(M)})$
- ABC SMC
 $\rightarrow P(M, \theta^{(1)}, \dots, \theta^{(M)}|D)$
- Marginalize
 $\rightarrow P(M|D)$

Model selection on a joint space

 M_1 M_2 M_3 M_4

(Toni and Stumpf, Bioinformatics, 2010)

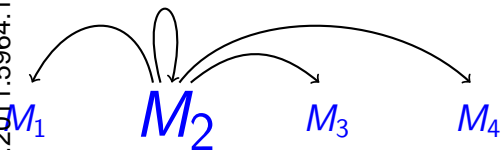
Model selection on a joint space

M_1 M_2 M_3 M_4

M^*

(Toni and Stumpf, Bioinformatics, 2010)

Model selection on a joint space

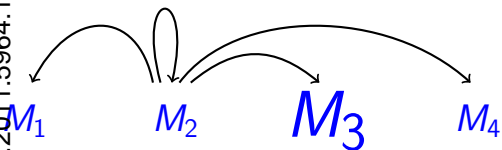


$$M^*$$

$$M^{**} \sim KM(M|M^*)$$

(Toni and Stumpf, Bioinformatics, 2010)

Model selection on a joint space



$$M^*$$

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Model selection on a joint space

(M_3, θ_3)
 (M_3, θ_7)
 (M_3, θ_6) (M_3, θ_2)
 (M_3, θ_8) (M_3, θ_5) (M_3, θ_1)
 (M_3, θ_4) (M_3, θ_9)

$$M^*$$

$$M^{**} \sim KM(M|M^*)$$

$$\theta^*$$

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 θ^*

$$\theta^{**} \sim KP(\theta|\theta^*)$$

Toni and Stumpf, Bioinformatics, 2010)

Model selection on a joint space

$$(M^{**}, \theta^{**})$$

$$M^*$$

$$M^{**} \sim KM(M|M^*)$$

$$\theta^*$$

$$\theta^{**} \sim KP(\theta|\theta^*)$$

accept / reject

(Toni and Stumpf, Bioinformatics, 2010)

Model selection on a joint space

$$w(M^{**}, \theta^{**})$$

$$M^*$$

$$M^{**} \sim KM(M|M^*)$$

$$\theta^*$$

$$\theta^{**} \sim KP(\theta|\theta^*)$$

accept / reject

calculate w

(Toni and Stumpf, Bioinformatics, 2010)

Model selection on joint space: Weight calculation

$$w_t(m^{**}, \theta^{**})$$

$$=$$

$$\pi(m^{**}, \theta^{**})$$

$$\underbrace{\sum_{j=1}^{\mathcal{M}} P_{t-1}^{(j)} KM_t(m^{**} | m_{t-1}^{(j)})}_{\text{model perturbation}} \underbrace{\sum_{k; m_{t-1}=m^{**}} \frac{w_{t-1}^{(k)}}{\sum_{l; m_{t-1}=m^{**}} w_{t-1}^{(l)}} KP_{t, m^{**}}(\theta^{**} | \theta_{t-1}^{(k)})}_{\text{parameter perturbation}}$$

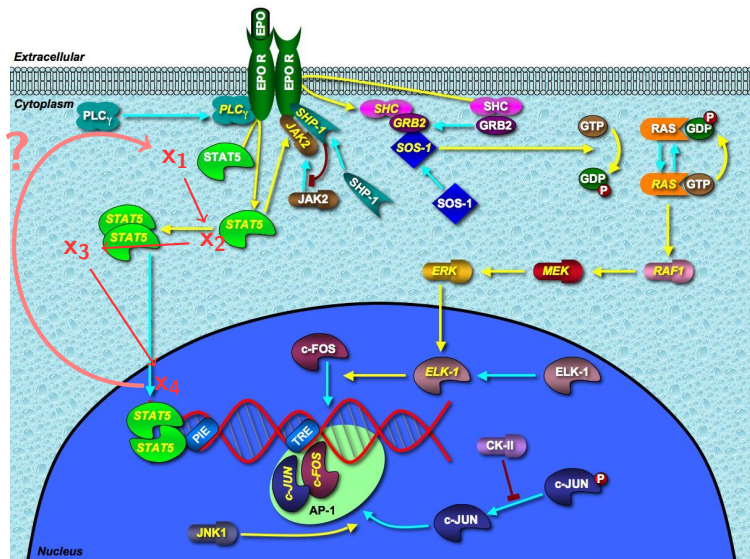
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Model selection: Epo signaling pathway

- Epo hormone synthesised when oxygen levels low
- Regulates red blood cell production
- Deliver oxygen to tissue
- Epo = "bloodbooster" (blood doping in endurance sports)



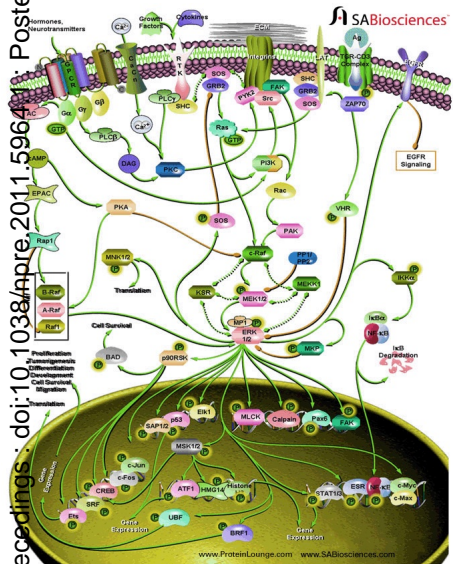
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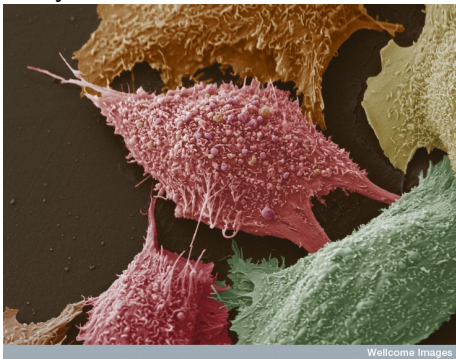
(adapted from Biocarta)

Precedings : doi:10.1038/npre.2011.5964.1

Erk signaling pathway



Erk signaling pathway relevant to many cancers.



Dual phosphorylation mechanisms

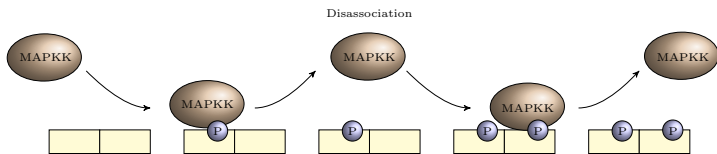


Figure 1: Distributive phosphorylation.

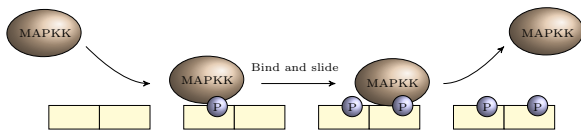


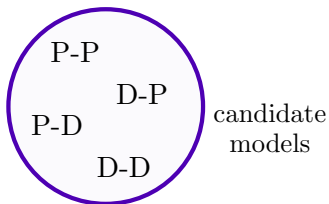
Figure 2: Processive phosphorylation.

Question

- *In vitro* phosphorylation MAPK is distributive (*Burack 1997, Ferrel 1997*).
- *In vitro* de-phosphorylation MAPK is distributive (*Zhao 2001*).
- Is it the same *in vivo*? Cannot study phosphorylation and dephosphorylation separately.

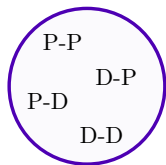
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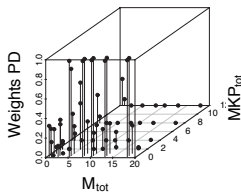
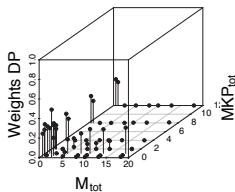
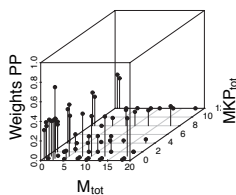
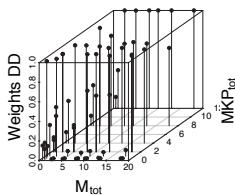
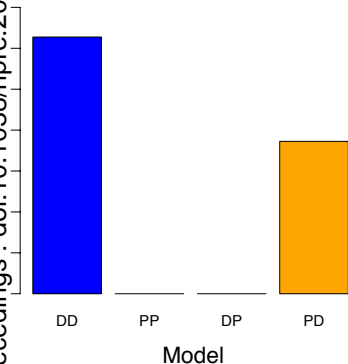


Model selection: Phosphorylation dynamics

Precedings: doi:10.1098/rspb.2011.5964.1 : Posted 13 May 2012



candidate models



Conclusion

- ABC methods are highly applicable in systems biology
 - 1 Prediction of dynamic behaviour
 - 2 Testing hypothesis about biological systems
- ABC SMC computationally efficient

Acknowledgements

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