MCMC Sampling for Intractable MJP Models of Chemical Kinetics via the Linear Noise Approximation

Mark A. Girolami

Department of Statistical Science
University College London

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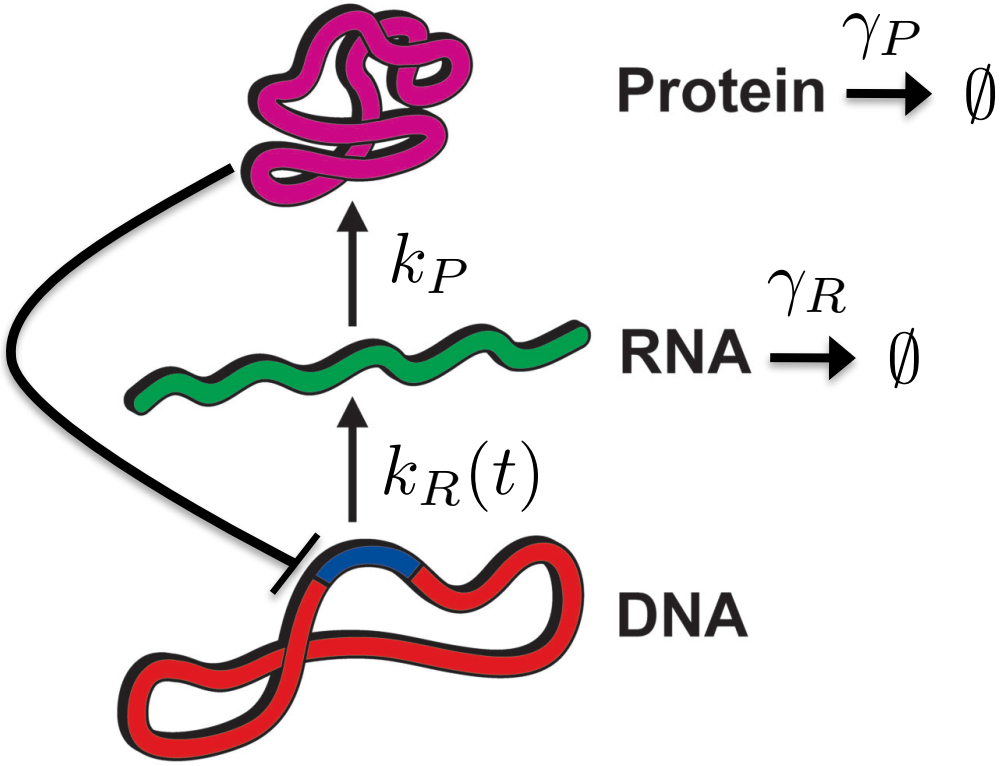
Outline

Single gene expression model



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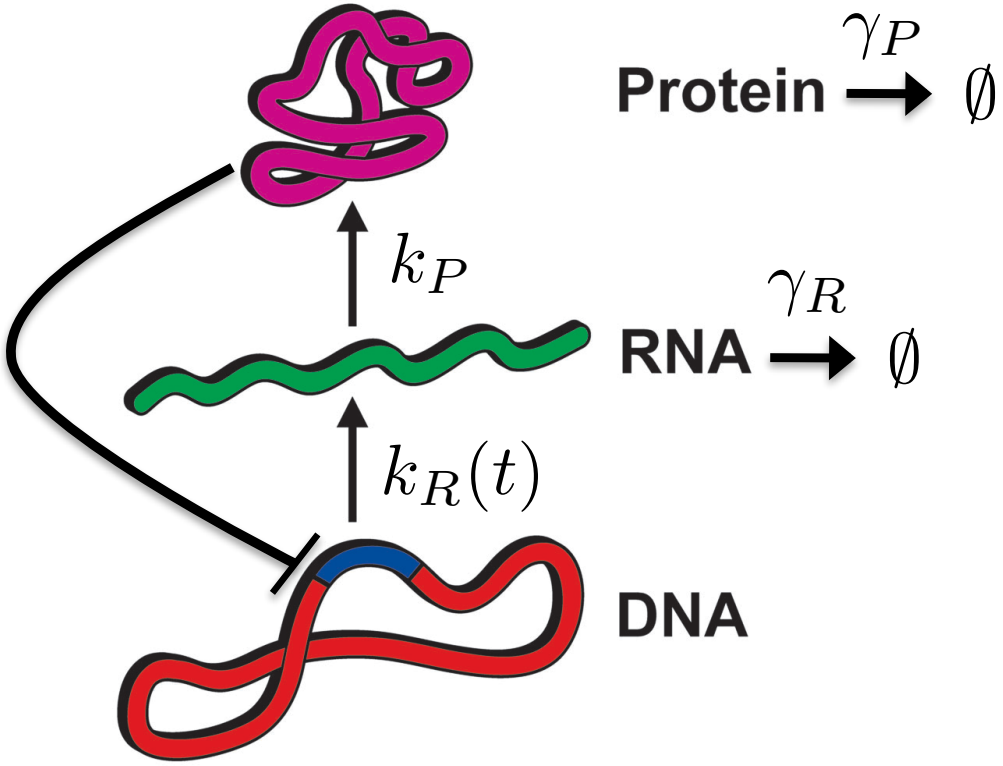

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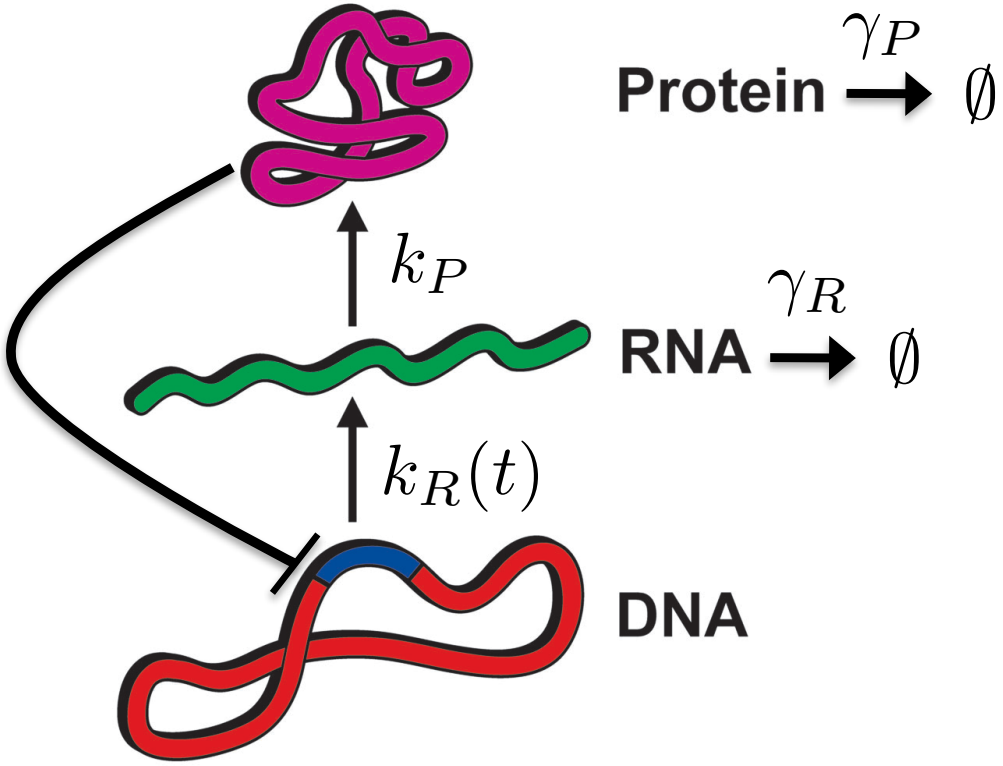

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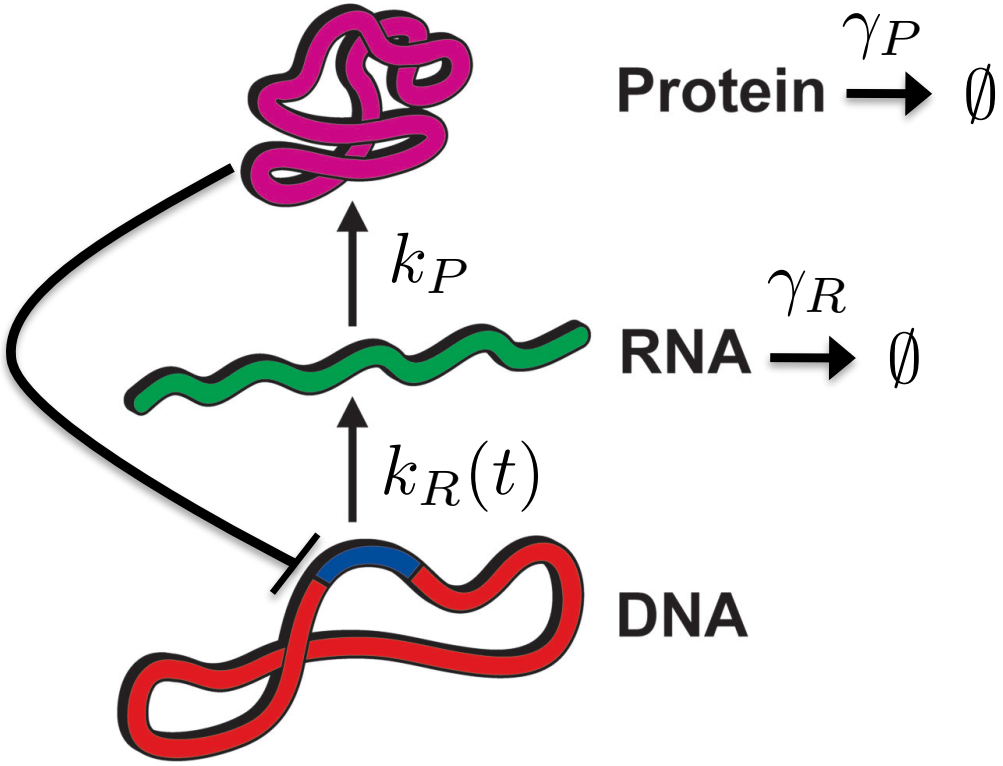

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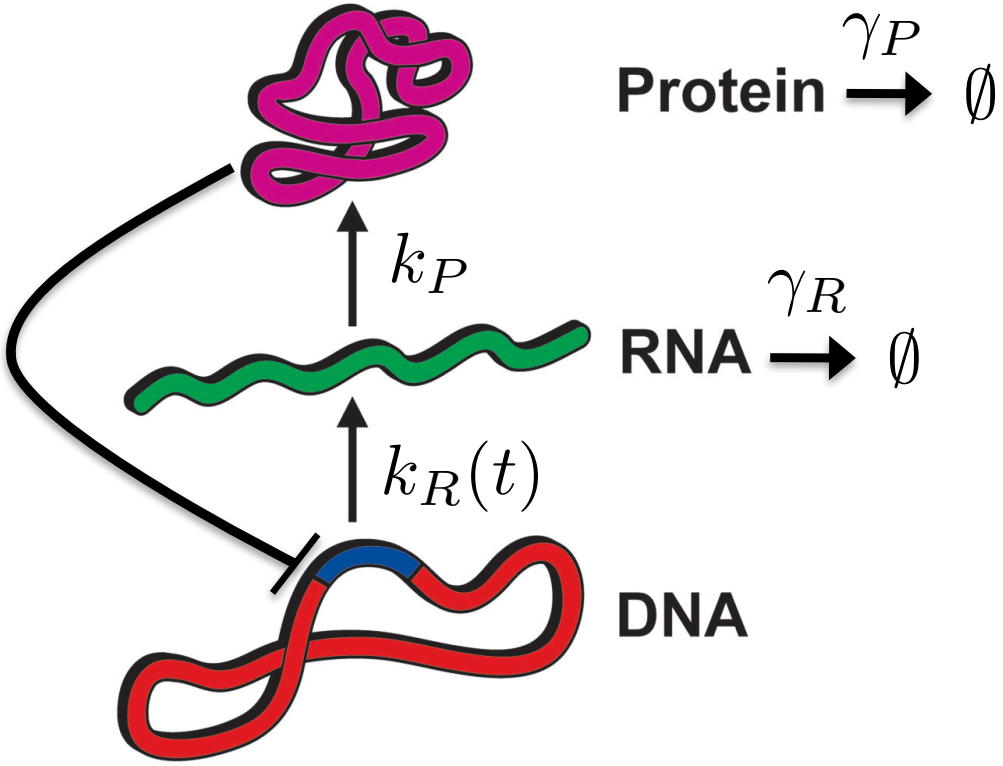

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- Parameter inference scheme Boys, Wilkinson, Kirkwood (2006)

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- Langevin Equation

$$d\boldsymbol{x}_t = \boldsymbol{S}\boldsymbol{f}(\boldsymbol{x}_t, \boldsymbol{\theta})dt + \frac{1}{\sqrt{\Omega}}\boldsymbol{S}\sqrt{\mathrm{diag}(\boldsymbol{f}(\boldsymbol{x}_t, \boldsymbol{\theta}))}dB_t \tag{3}$$

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- Employed extensively in chemical physics and genome research
- May provide intermediate scheme for MCMC based inference

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- which is a linear SDE with analytic solution

$$\boldsymbol{\xi}_t = \boldsymbol{\Phi}(t_0, t)\left(\boldsymbol{\xi}_0 + \int_{t0}^{t}\boldsymbol{\Phi}(s, t)^{-1}\boldsymbol{S}\sqrt{\text{diag}(\boldsymbol{f}(\phi_s, \boldsymbol{\theta}))}dB_s\right)$$

- where $\boldsymbol{\Phi}(t0, s)$ the solution to

$$d\boldsymbol{\Phi}(t0, s) = \boldsymbol{S}\boldsymbol{J}_{\boldsymbol{f}}(\phi_s, \boldsymbol{\theta})\boldsymbol{\Phi}(t0, s)ds, \;\; \boldsymbol{\Phi}(t0, t0) = \boldsymbol{I}$$

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$$FI(\boldsymbol{\theta})_{m,n} = \frac{\partial \boldsymbol{\mu}(\boldsymbol{\theta})^T}{\partial \theta_m}\boldsymbol{\Sigma}^{-1}(\boldsymbol{\theta})\frac{\partial \boldsymbol{\mu}(\boldsymbol{\theta})}{\partial \theta_n} + \frac{1}{2}\text{tr}\left(\boldsymbol{\Sigma}^{-1}(\boldsymbol{\theta})\frac{\partial \boldsymbol{\Sigma}(\boldsymbol{\theta})}{\partial \theta_m}\boldsymbol{\Sigma}^{-1}(\boldsymbol{\theta})\frac{\partial \boldsymbol{\Sigma}(\boldsymbol{\theta})}{\partial \theta_n}\right)$$

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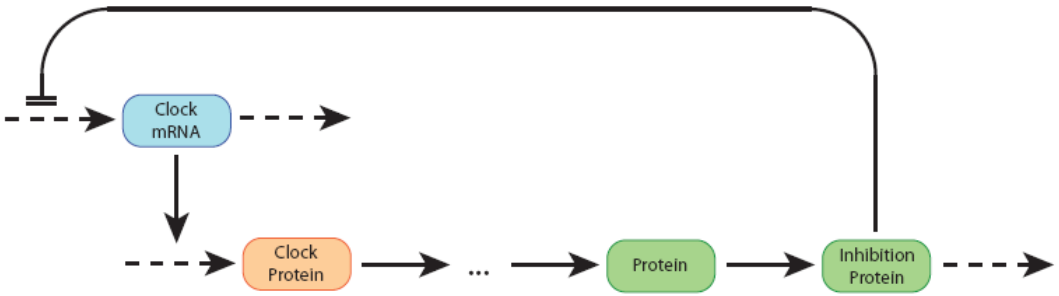
- Augment the MRE for ϕ with the lower triangular elements of $\boldsymbol{V}$ and solve the augmented system with forward sensitivity analysis.

Mechanistic Models

Mechanistic modelling



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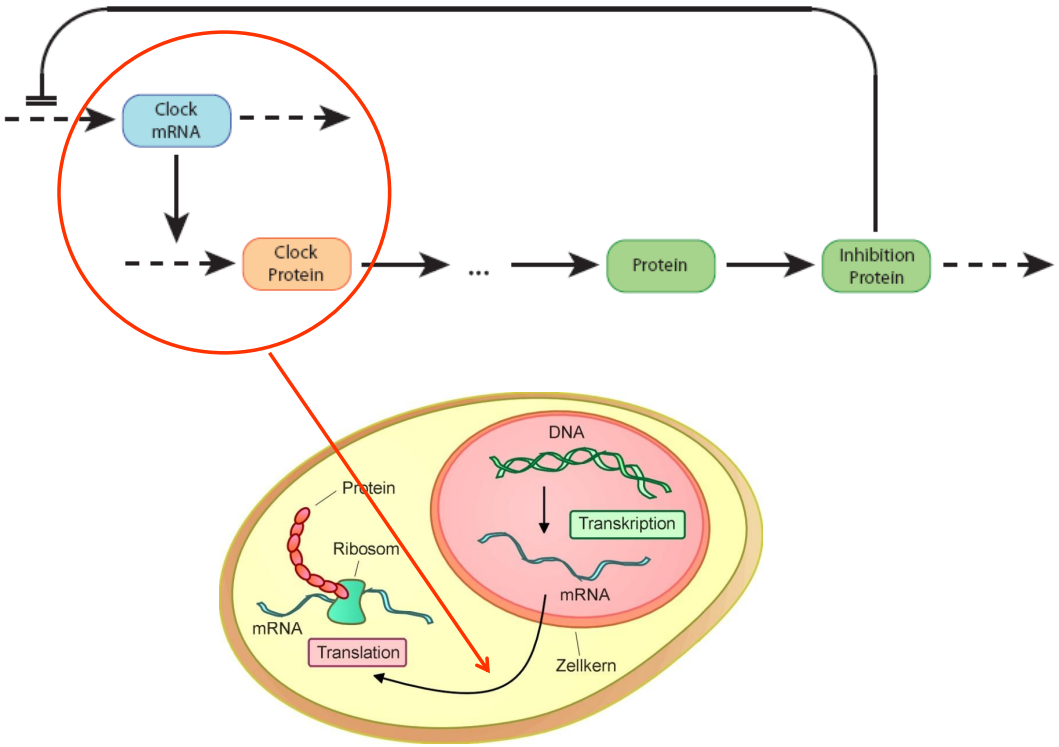

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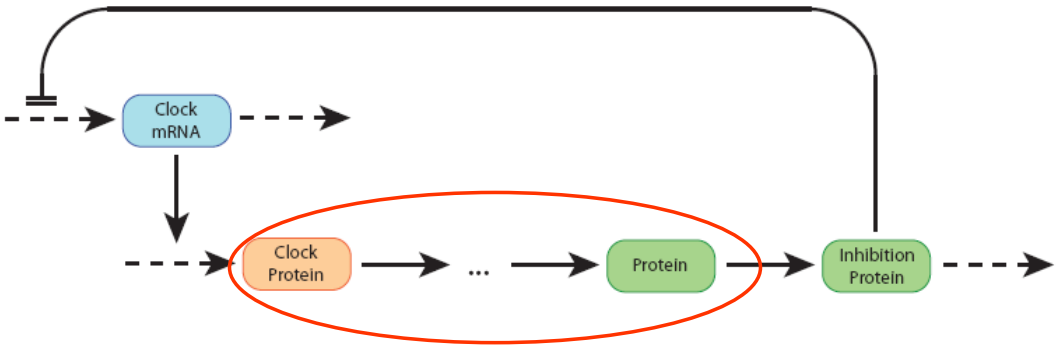

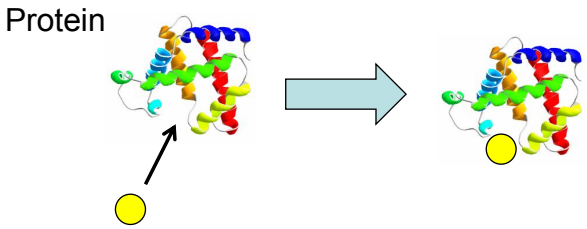

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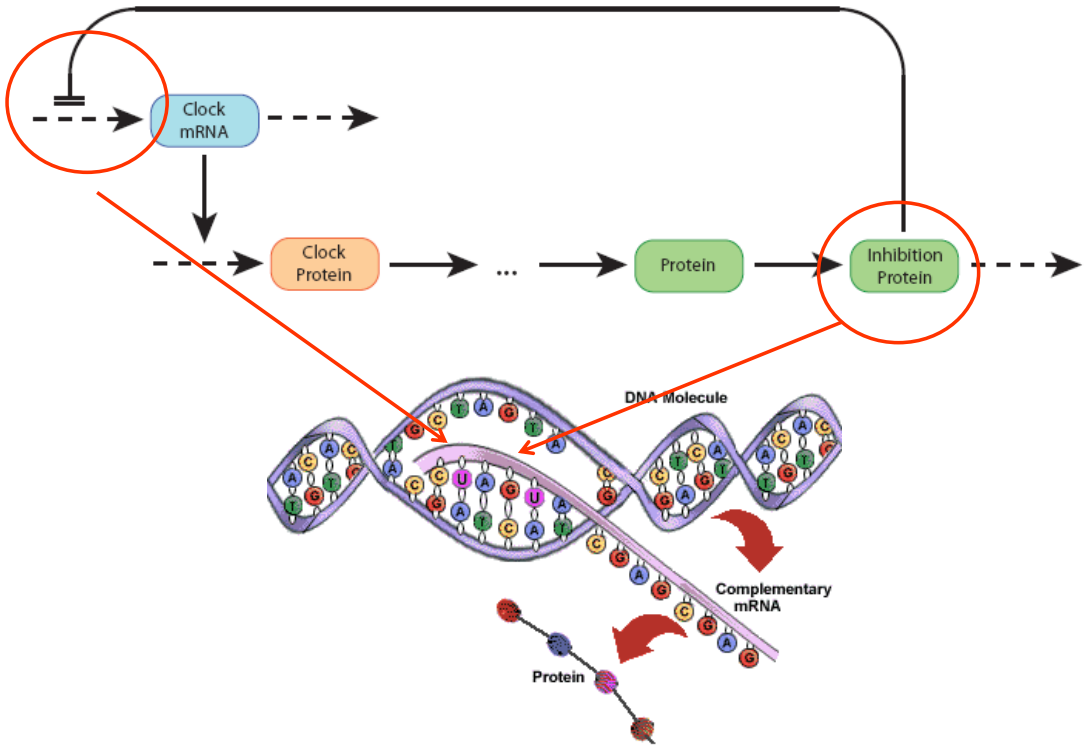

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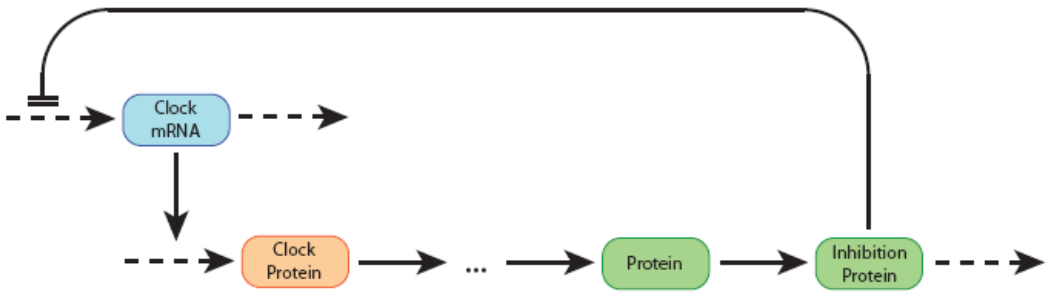

Figure: A diagram of the Goodwin Circadian Oscillator model network.

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Mechanistic Models

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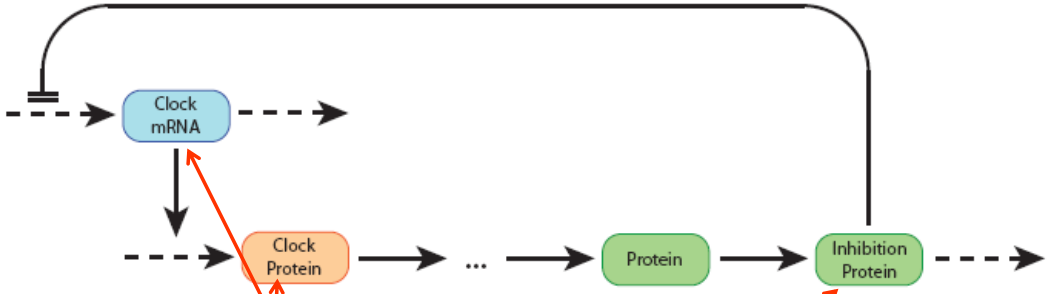

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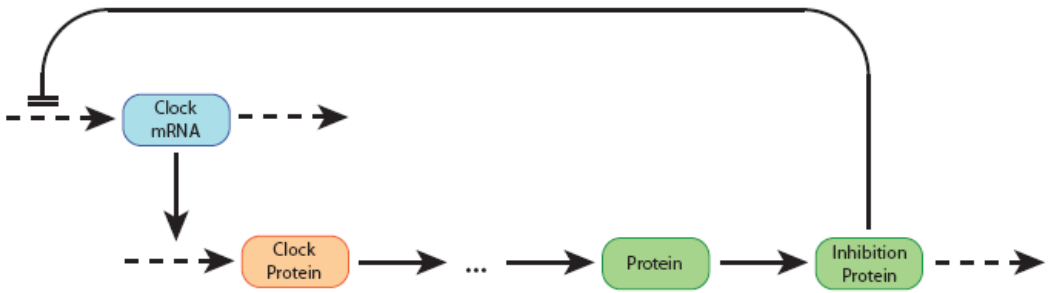

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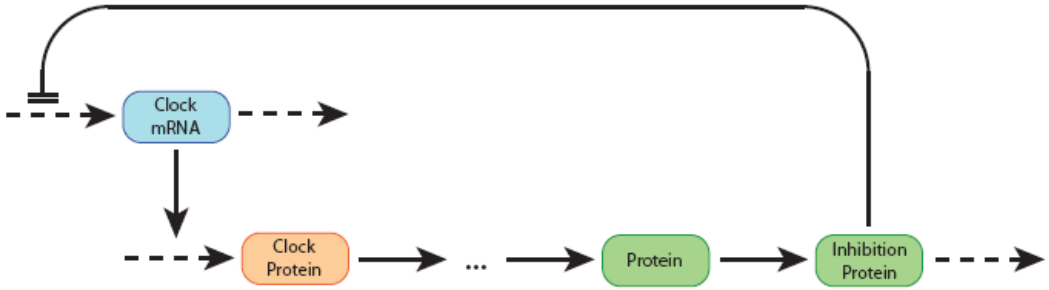

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Dependence on kinetic parameters → $\boldsymbol{\theta}$

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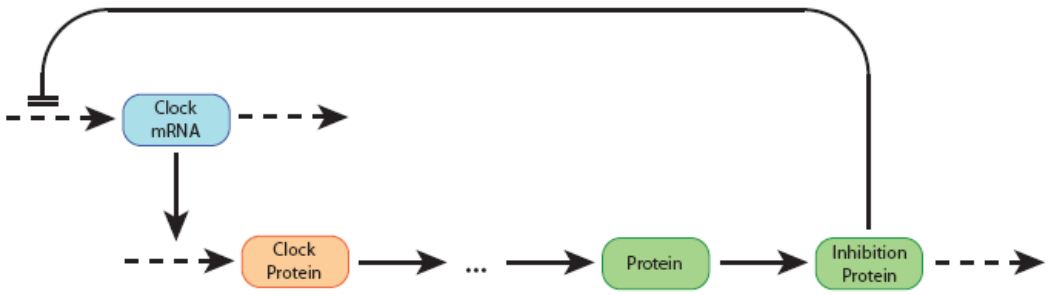
Mechanistic Models

Necessary condition for stable oscillations



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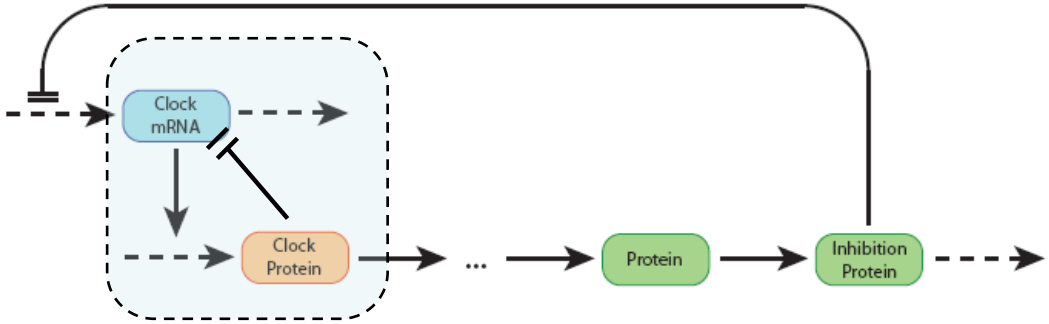
> 2

> 8

Mechanistic Models

Example: log likelihood landscape



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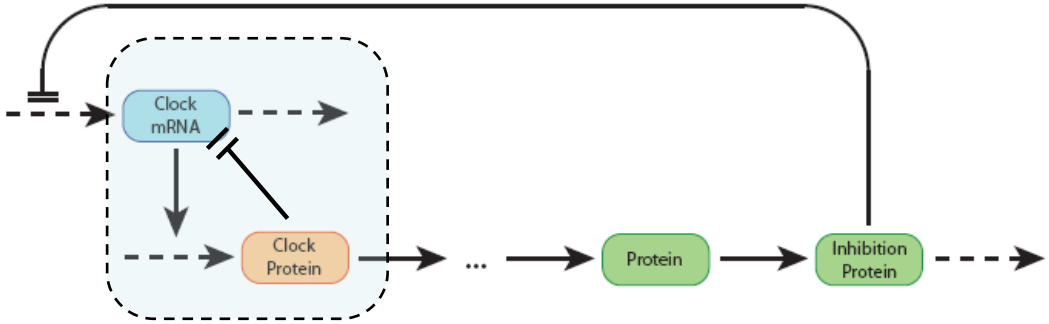

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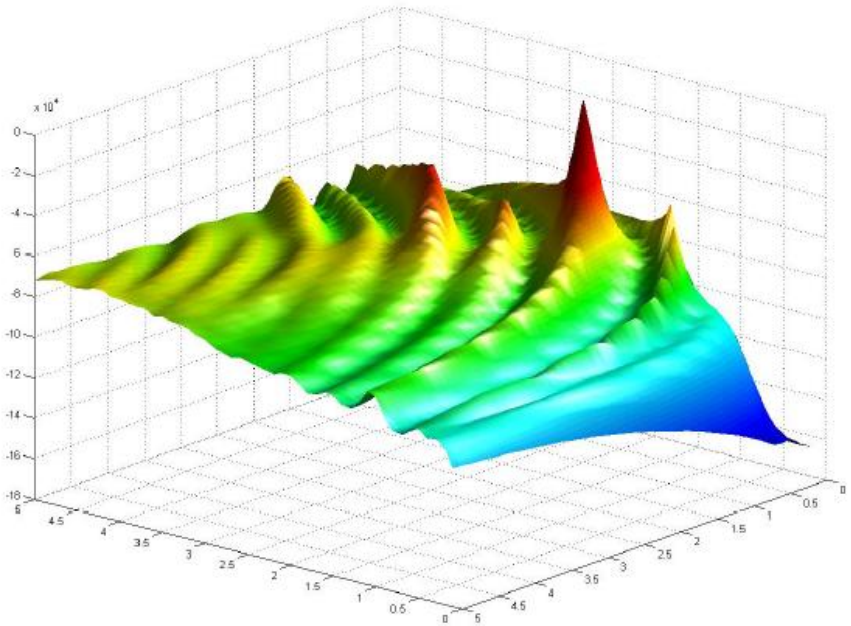
2 parameters free,
others fixed

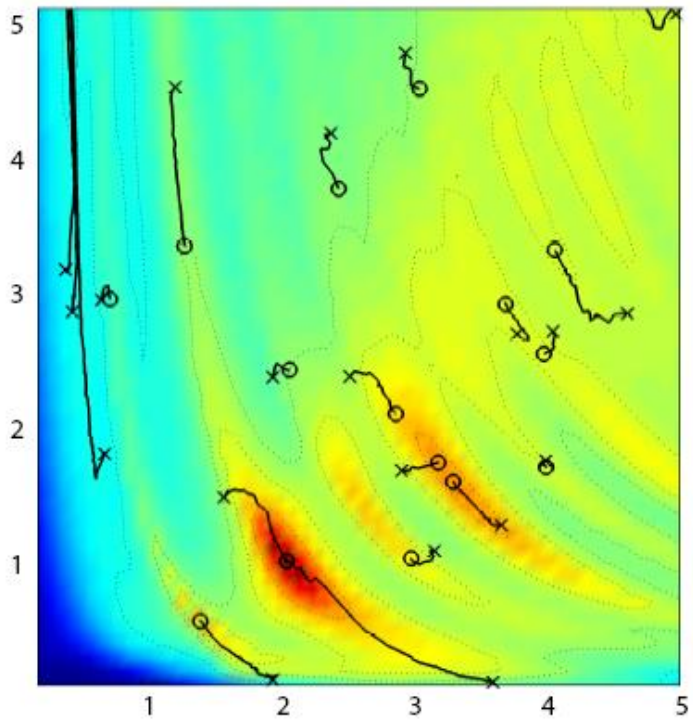
Mechanistic Models

Posterior landscape $P(\boldsymbol{\theta}|\mathcal{M}, \mathcal{D})$



Mechanistic Models

MCMC trajectories



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SERIES B
Statistical
Methodology

J. R. Statist. Soc. B (2011)
73, *Part* 2, *pp.* 123–214

Riemann manifold Langevin and Hamiltonian Monte Carlo methods

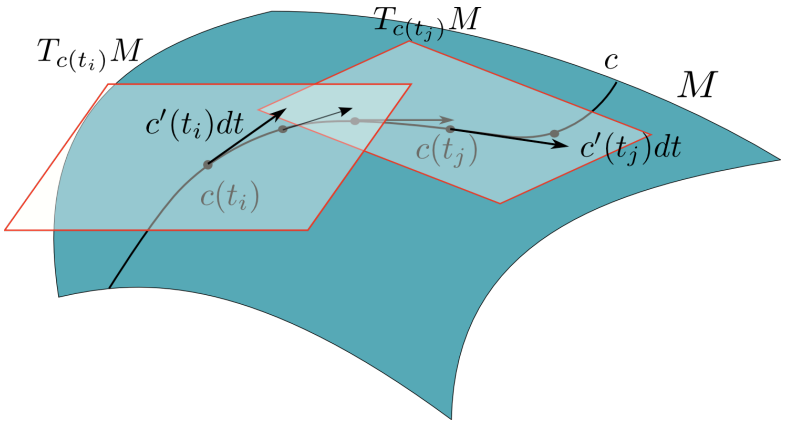
Mark Girolami and Ben Calderhead

University College London, UK

[*Read before* The Royal Statistical Society *at a meeting organized by the* Research Section *on Wednesday, October 13th, 2010*, Professor D. M. Titterington *in the Chair*]

Summary. The paper proposes Metropolis adjusted Langevin and Hamiltonian Monte Carlo sampling methods defined on the Riemann manifold to resolve the shortcomings of existing Monte Carlo algorithms when sampling from target densities that may be high dimensional and exhibit strong correlations. The methods provide fully automated adaptation mechanisms that circumvent the costly pilot runs that are required to tune proposal densities for Metropolis–Hastings or indeed Hamiltonian Monte Carlo and Metropolis adjusted Langevin algorithms. This allows for highly efficient sampling even in very high dimensions where different scalings may be required for the transient and stationary phases of the Markov chain. The methodology proposed exploits the Riemann geometry of the parameter space of statistical models and thus automat-

Geometric Concepts in MCMC



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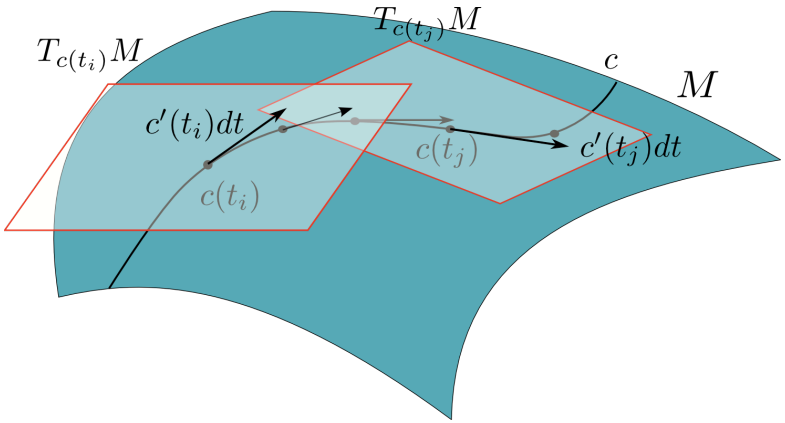

- Tangent space - local metric defined by $\delta\boldsymbol{\theta}^{\mathsf{T}}\mathbf{G}(\boldsymbol{\theta})\delta\boldsymbol{\theta} = g_{kl}\delta\theta_k\delta\theta_l$

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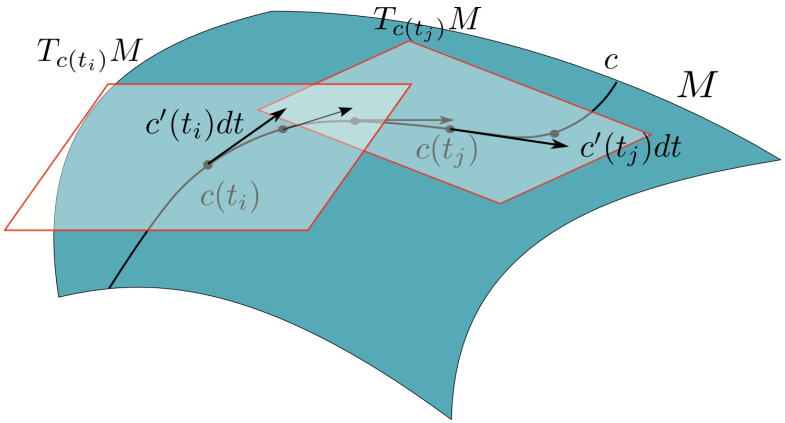

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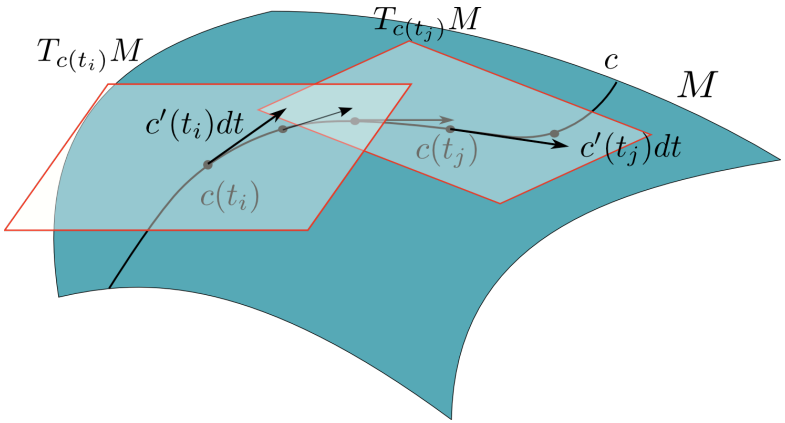

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$$\Gamma^i_{kl} = \frac{1}{2}\sum_m g^{im}\left(\frac{\partial g_{mk}}{\partial\theta^l} + \frac{\partial g_{ml}}{\partial\theta^k} - \frac{\partial g_{kl}}{\partial\theta^m}\right)$$

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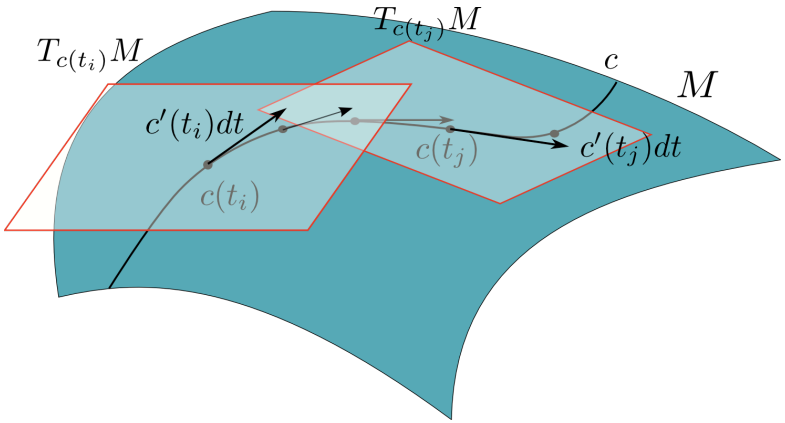

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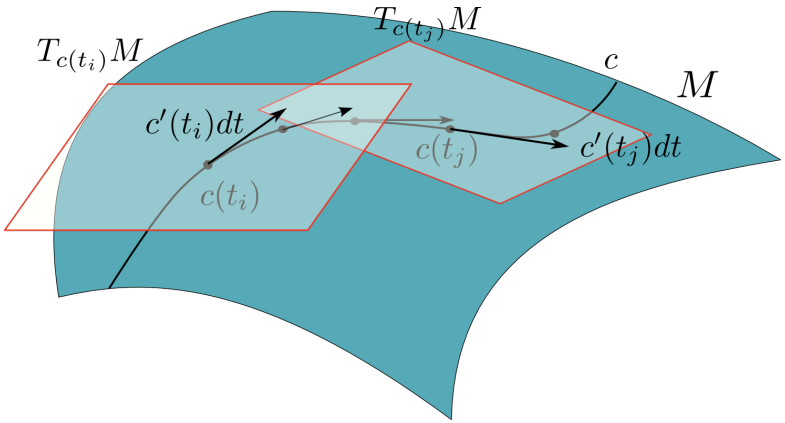

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$$\frac{d^2\theta^i}{dt^2} + \sum_{k,l}\Gamma^i_{kl}\frac{d\theta^k}{dt}\frac{d\theta^l}{dt} = 0$$

Illustration of Geometric Concepts

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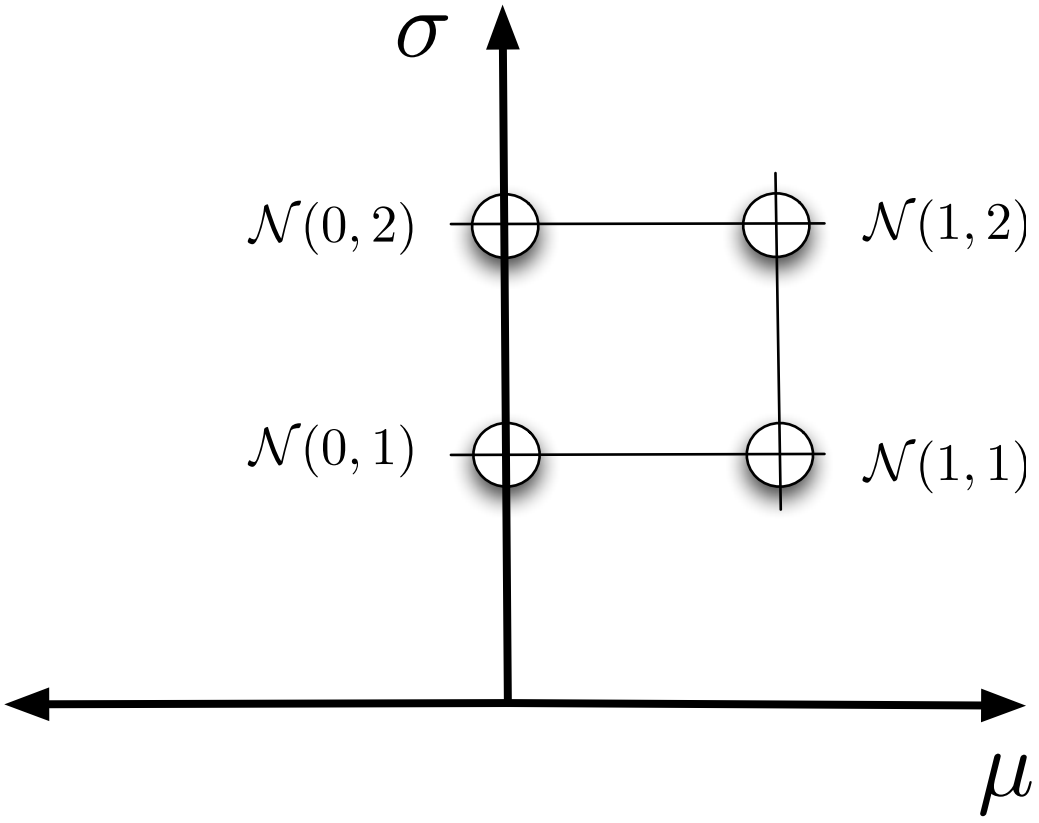
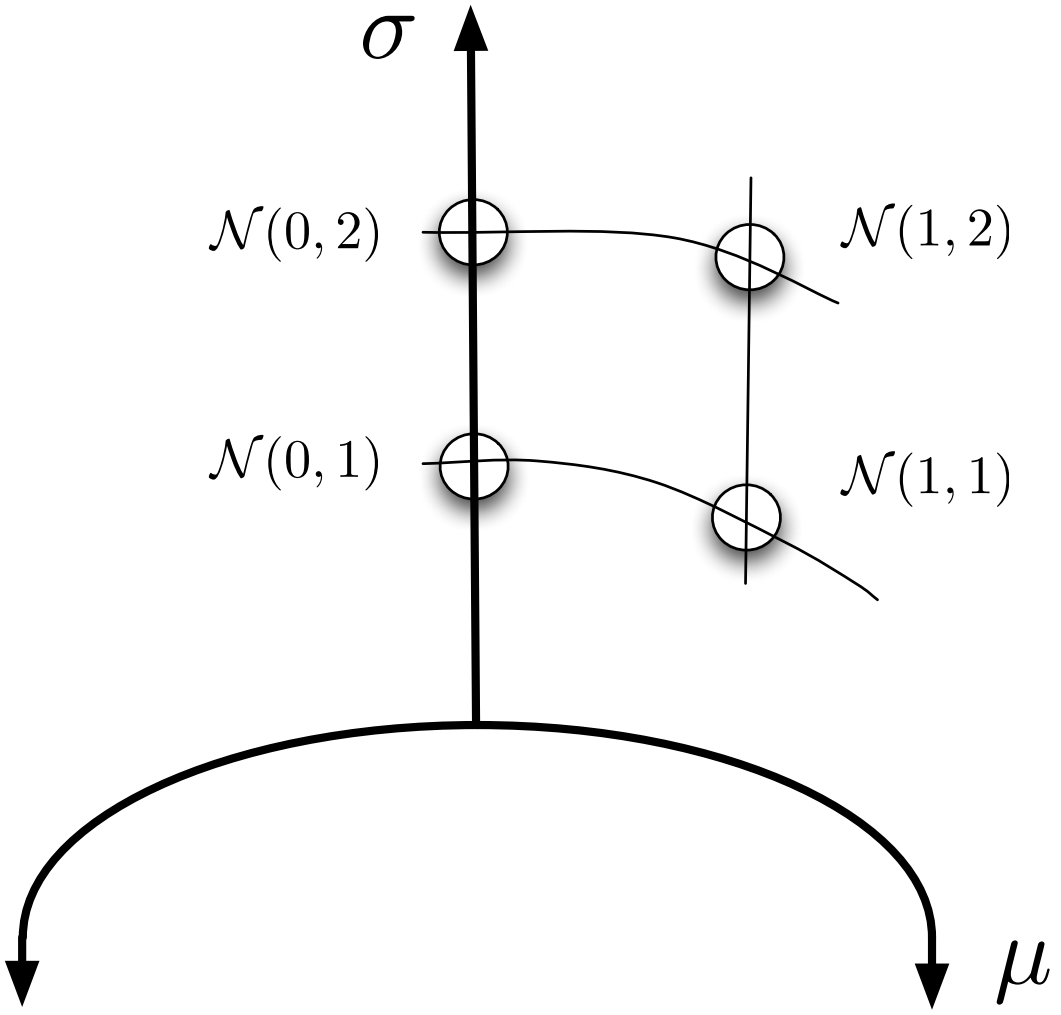
- Consider densities $\mathcal{N}(0, 1)$ & $\mathcal{N}(1, 1)$ and $\mathcal{N}(0, 2)$ & $\mathcal{N}(1, 2)$

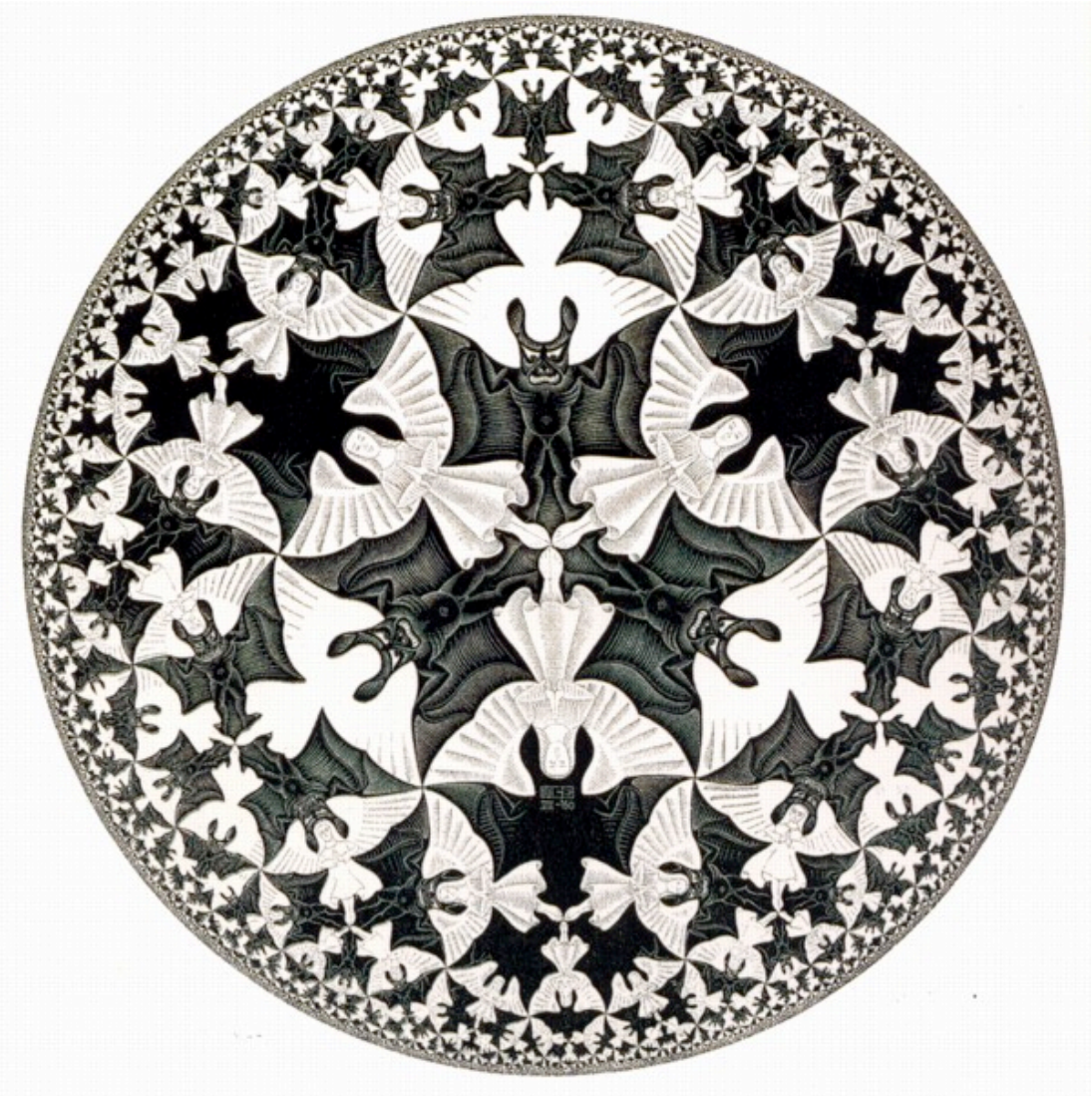
Normal Density - Euclidean Parameter space



Normal Density - Riemannian Functional space



M.C. Escher, Heaven and Hell, 1960



Langevin Diffusion on Riemannian manifold

- Discretised Langevin diffusion on manifold defines proposal mechanism

$$\theta'_d = \theta_d + \frac{\epsilon^2}{2}\left(\boldsymbol{G}^{-1}(\theta)\nabla_\theta \mathcal{L}(\theta)\right)_d - \epsilon^2 \sum_{i,j}^{D} \boldsymbol{G}(\theta)^{-1}_{ij}\Gamma^d_{ij} + \epsilon\left(\sqrt{\mathbf{G}^{-1}(\theta)}\mathbf{z}\right)_d$$

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$$p_p(\theta'|\theta) = \mathcal{N}(\theta'|\boldsymbol{\mu}(\theta,\epsilon), \epsilon^2\mathbf{G}^{-1}(\theta))$$

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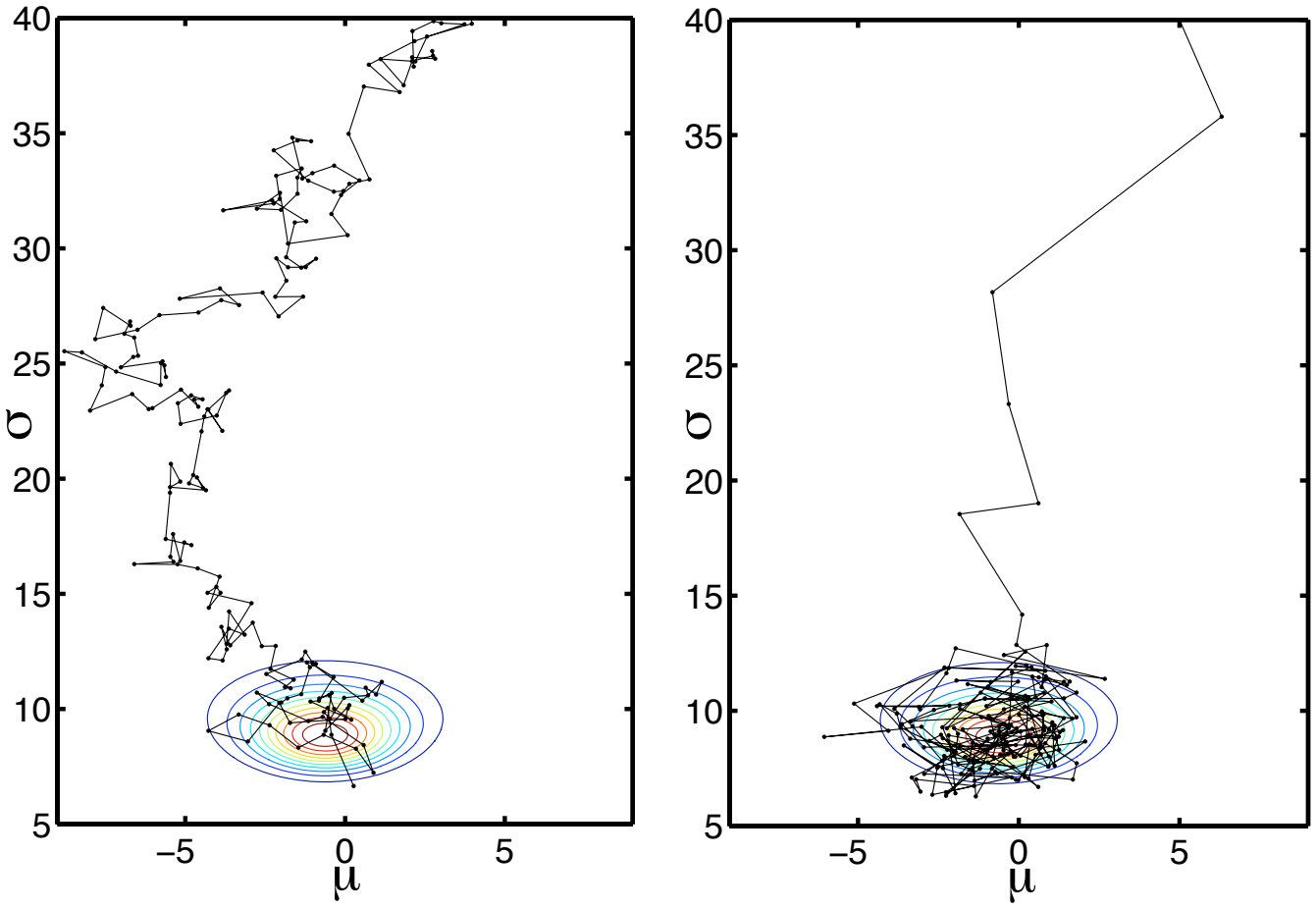
- Proposal mechanism diffuses approximately along the manifold

Langevin Diffusion on Riemannian manifold



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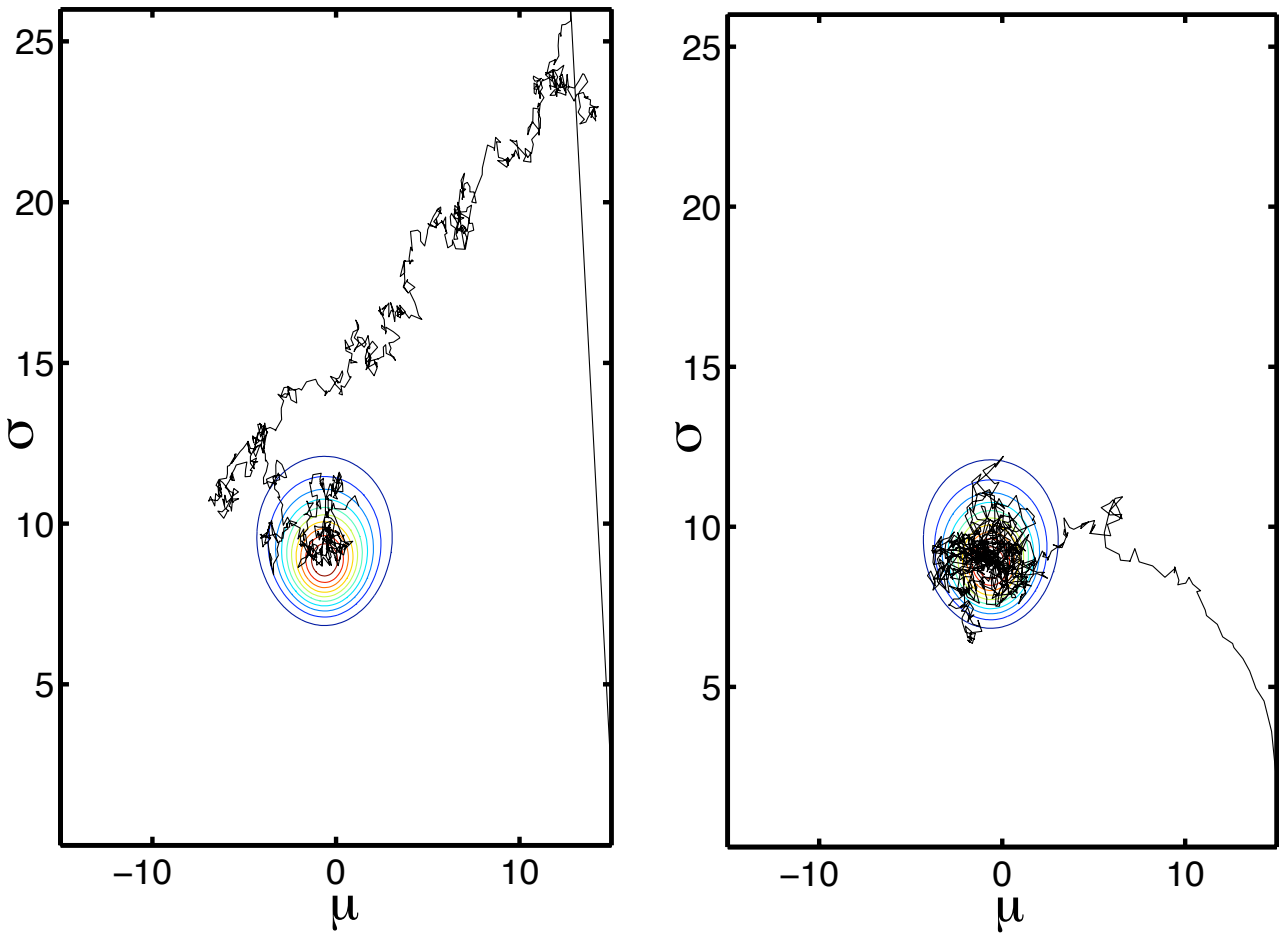

Simplified Manifold MALA

- For $\boldsymbol{\theta} \in \mathbb{R}^D$ with density $\pi(\boldsymbol{\theta})$, $\mathcal{L}(\boldsymbol{\theta}) \equiv \log \pi(\boldsymbol{\theta})$
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$$\boldsymbol{\mu}(\boldsymbol{\theta}, \epsilon) = \boldsymbol{\theta} + \frac{\epsilon^2}{2}\left(\mathbf{G}^{-1}(\boldsymbol{\theta})\nabla_{\boldsymbol{\theta}}\mathcal{L}(\boldsymbol{\theta})\right), \quad \mathbf{G}^{-1}(\boldsymbol{\theta}) = FI(\boldsymbol{\theta})$$

Simplified Manifold MALA

- For $\boldsymbol{\theta} \in \mathbb{R}^D$ with density $\pi(\boldsymbol{\theta})$, $\mathcal{L}(\boldsymbol{\theta}) \equiv \log \pi(\boldsymbol{\theta})$
- Define proposal distribution

$$q(\boldsymbol{\theta}^*|\boldsymbol{\theta}^{t-1}) = \mathcal{N}\left(\boldsymbol{\theta}^*|\boldsymbol{\mu}(\boldsymbol{\theta}^{t-1}, \epsilon), \epsilon^2 \mathbf{G}^{-1}(\boldsymbol{\theta}^{t-1})\right)$$

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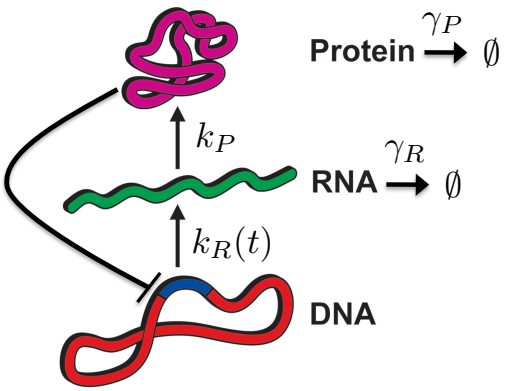
- Accept $\boldsymbol{\theta}^*$ with probability

$$\min\left\{1, \frac{\pi(\boldsymbol{\theta}^*)}{\pi(\boldsymbol{\theta}^{t-1})}\frac{q(\boldsymbol{\theta}^{t-1}|\boldsymbol{\theta}^*)}{q(\boldsymbol{\theta}^*|\boldsymbol{\theta}^{t-1})}\right\}$$

Single gene expression model



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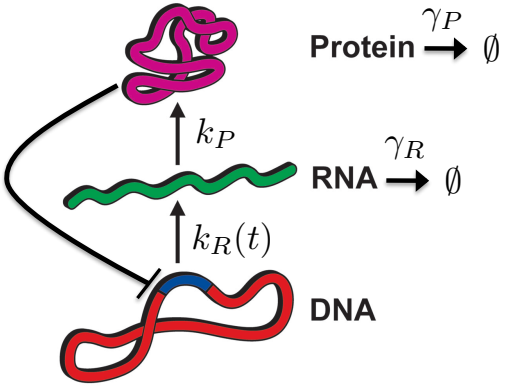

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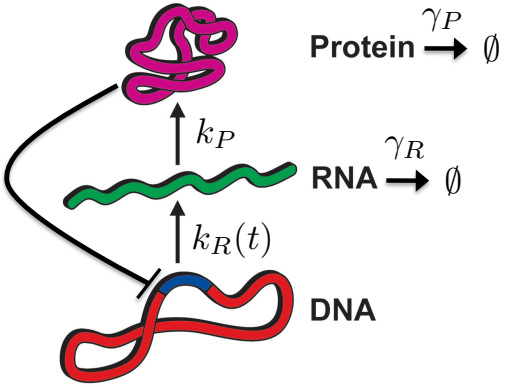

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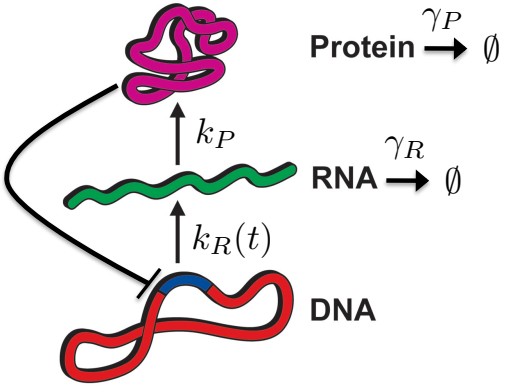

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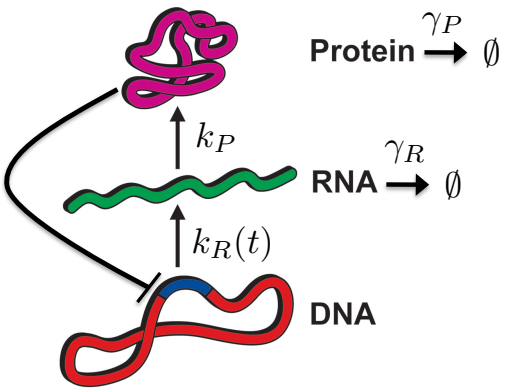

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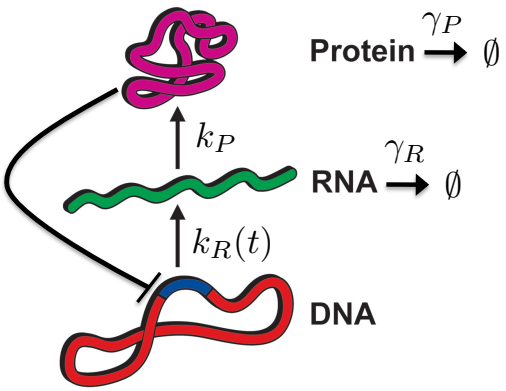

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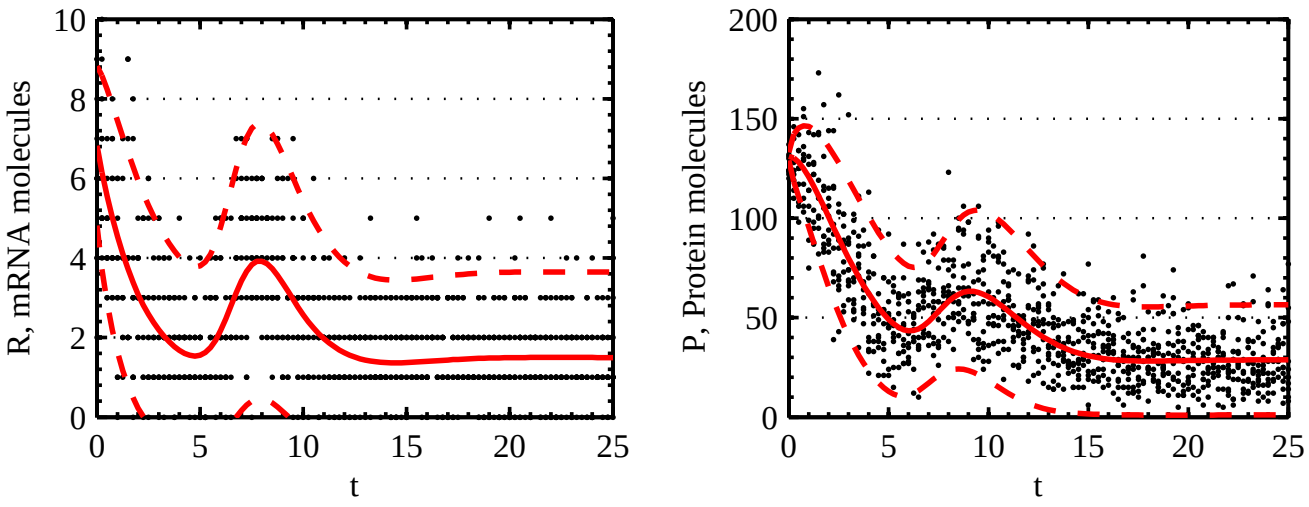
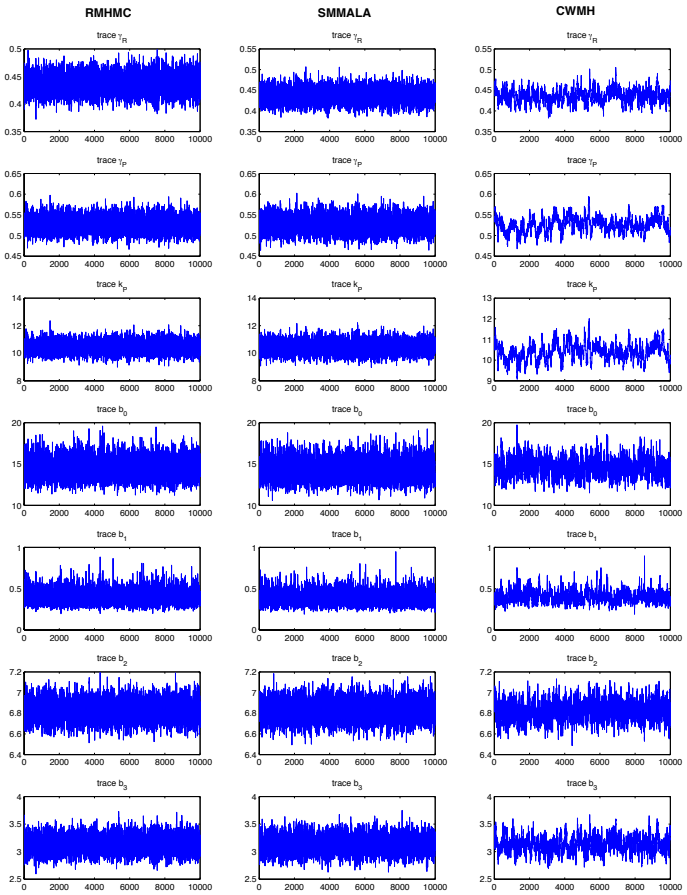
Simulated Data



- Simulated data generated with SSA.
- 10 independent sample paths for each time point.
- Parameters set to

γ_R	γ_P	k_P	b_0	b_1	b_2	b_3
0.44	0.52	10.0	15.0	0.40	7.0	3.0

Trace Plots


RMHMC
SMMALA
CWMH
trace γ_R
trace γ_P
trace k_P
trace b_0
trace b_1
trace b_2
trace b_3

Effective Sample Size

10,000 posterior samples

	γ_R	γ_P	k_P	b_0	b_1	b_2	b_3
RMHMC	6532	6593	6614	5112	5384	6595	6642
SMMALA	2990	3270	3454	3124	3164	3316	3195
CWMH	201	71	73	465	339	420	239

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- Assume initial conditions known $S_1(t_0) = 5\Omega$, $S_2(t_0) = S_3(t_0) = 0$, $t_0 = 0$. Reaction rate parameters to $c_1 = 1$, $\hat{c}_2 = 2\Omega^{-1}$, $c_3 = 0.5$ and $c_4 = 0.04$

Effects of System Size

min. ESS vs. Ω

Ω	M.H.	SMMALA	RMHMC
1	121 (3.6)	150 (3.9)	245 (0.06)
2	226 (6.7)	2163 (57.2)	4775 (1.3)
5	132 (3.9)	3539 (93.6)	4618 (1.2)
10	180 (5.3)	3397 (89.8)	5954 (1.6)
100	214 (6.4)	3725 (98.5)	6066 (1.7)

Posterior mean and SD. vs. Ω

Ω	c_1	$\hat{c}_2$	c_3	c_4
1	0.88 (0.031)	1.72 (0.253)	0.39 (0.039)	0.003 (0.002)
2	1.3 (0.041)	0.69 (0.066)	0.35 (0.016)	0.014 (0.002)
5	0.93 (0.019)	0.39 (0.028)	0.48 (0.025)	0.034 (0.002)
10	1.0 (0.015)	0.18 (0.008)	0.47 (0.015)	0.037 (0.001)
100	0.99 (0.004)	0.01 (0.0002)	0.52 (0.004)	0.039 (0.0003)

Failure Modes

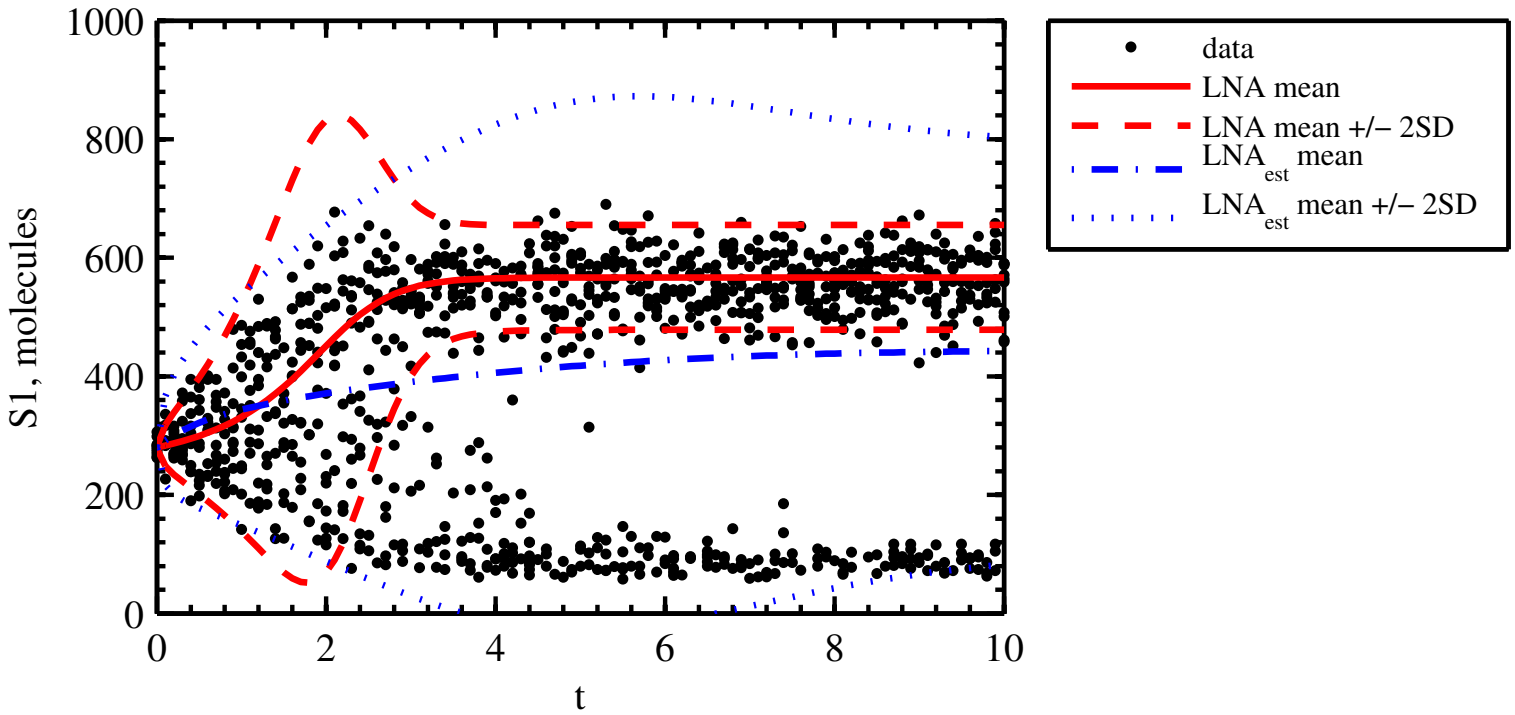

Figure: Simulated time point data using SSA for the Schlögl reaction set and LNA predictions. Dots correspond to simulated data. The bold and dashed red lines correspond to the LNA prediction for the means and standard deviations using the true parameters. Doted blue lines correspond the LNA predictions using the posterior means for the rate parameters. (Online version in colour.)

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