Statistical Inference for Markov Jump Processes via Differential Geometric Monte Carlo and the LNA

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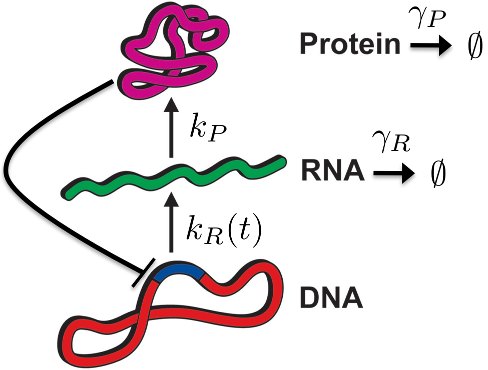
Outline

Single gene expression model



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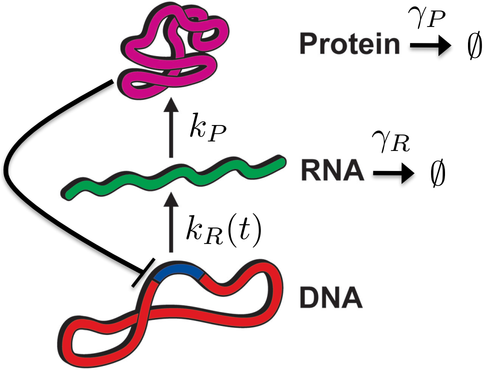

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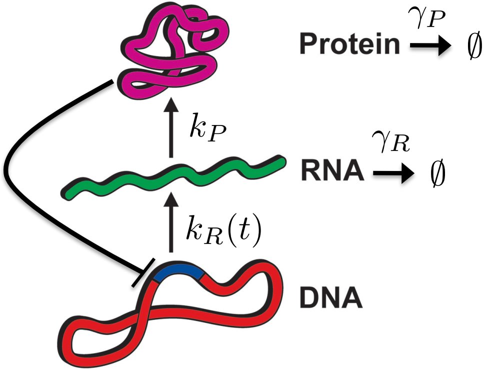

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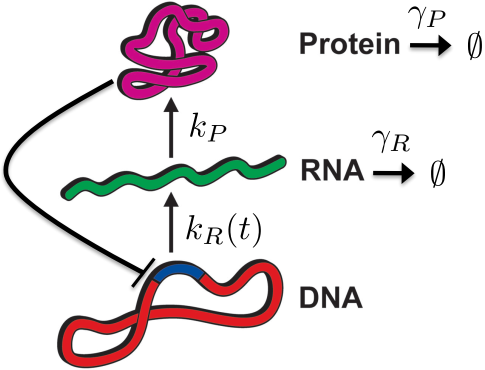

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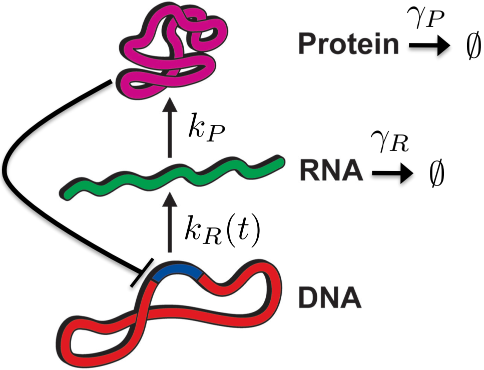

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- $\boldsymbol{\theta} = (\gamma_R, \gamma_P, k_P, b_0, b_1, b_2, b_3)$

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- Intractible, simulate trajectories by a Stochastic Simulation Algorithm.

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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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- which is a linear SDE with analytic solution

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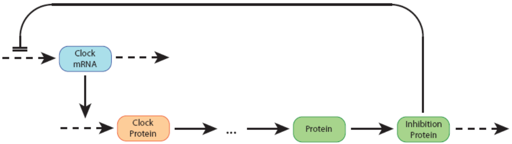
- Augment the MRE for ϕ with the lower triangular elements of $\boldsymbol{V}$ and solve the augmented system with forward sensitivity analysis.

Mechanistic Models

Mechanistic modelling



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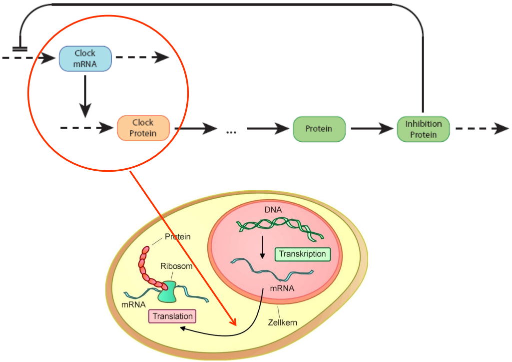

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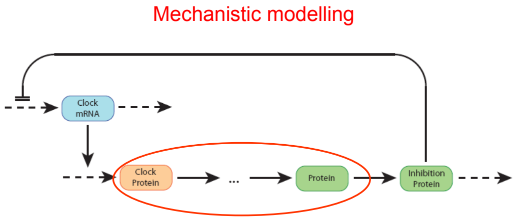

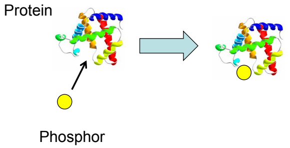

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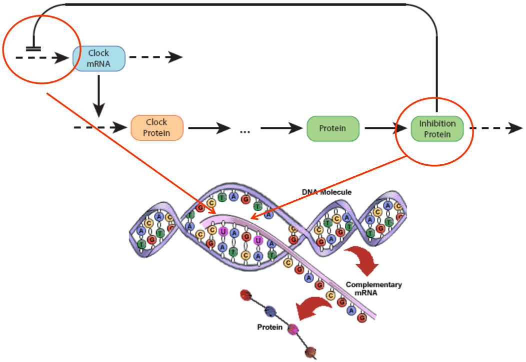

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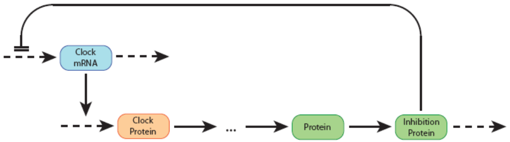

Figure: A diagram of the Goodwin Circadian Oscillator model network.

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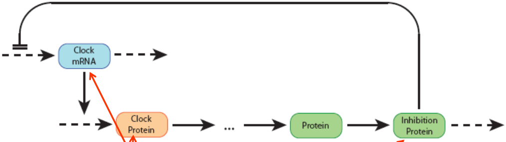

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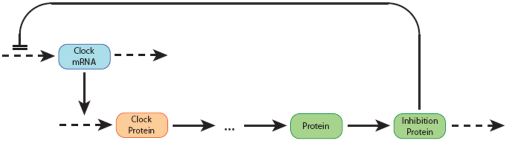

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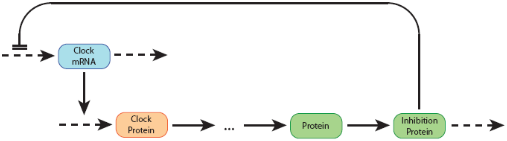

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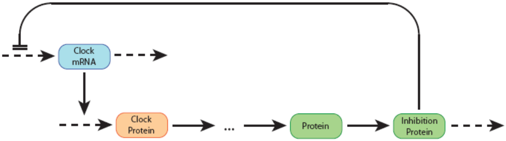
Mechanistic Models

Necessary condition for stable oscillations



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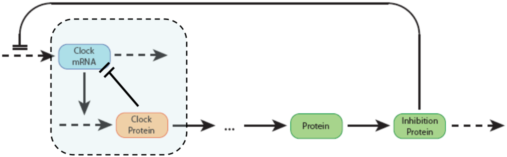
Mechanistic Models

Example: log likelihood landscape



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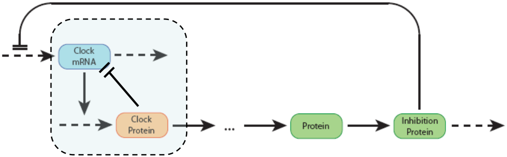

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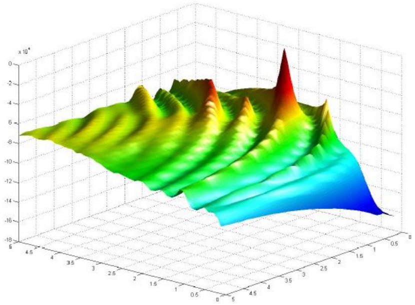
$$

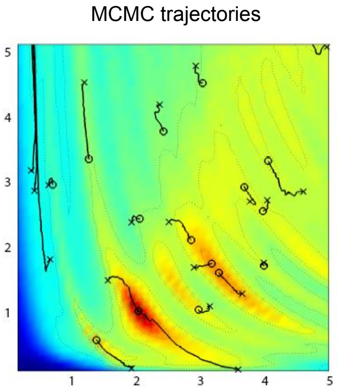
2 parameters free,
others fixed

Mechanistic Models

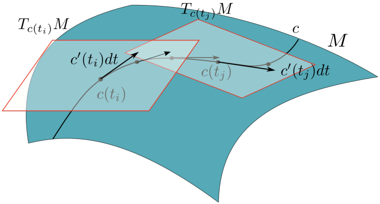
Posterior landscape $P(\boldsymbol{\theta}|\mathcal{M},\mathcal{D})$



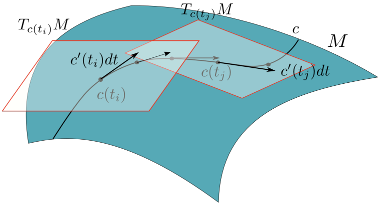
Mechanistic Models



Geometric Concepts in MCMC

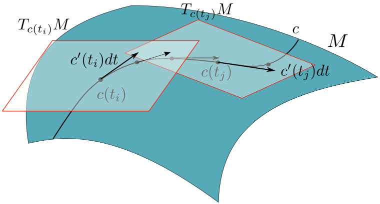


Geometric Concepts in MCMC



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

Geometric Concepts in MCMC



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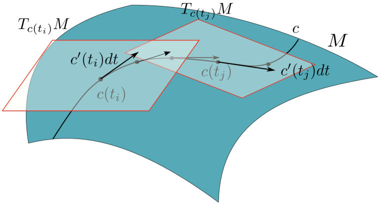

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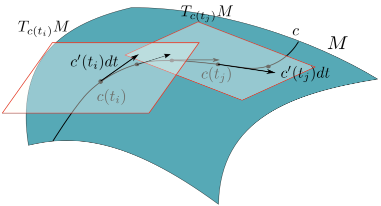
$$\Gamma^i_{kl} = \frac{1}{2}\sum_m g^{im}\left(\frac{\partial g_{mk}}{\partial\theta^l} + \frac{\partial g_{ml}}{\partial\theta^k} - \frac{\partial g_{kl}}{\partial\theta^m}\right)$$

Geometric Concepts in MCMC



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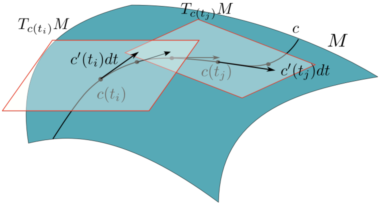

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$$\frac{d^2\theta^i}{dt^2} + \sum_{k,l}\Gamma^i_{kl}\frac{d\theta^k}{dt}\frac{d\theta^l}{dt} = 0$$

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Riemann manifold Langevin and Hamiltonian Monte Carlo methods

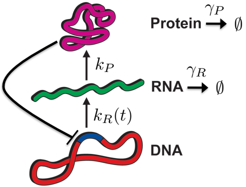
Mark Girolami and Ben Calderhead

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*]

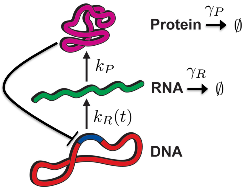
Summary. The paper proposes Metropolis adjusted Langevin and Hamiltonian Monte Carlo sampling methods defined on the Riemann manifold to resolve the shortcomings of existing Monte Carlo algorithms when sampling from target densities that may be high dimensional and exhibit strong correlations. The methods 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-

Single gene expression model



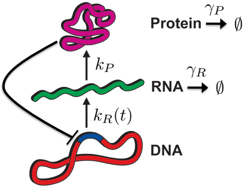
- Single gene expression model with negative feedback.

Single gene expression model



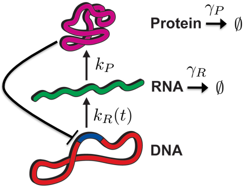
- Single gene expression model with negative feedback.
- System state $(R(t), P(t))^T$ models the population of RNA and protein.

Single gene expression model



- Single gene expression model with negative feedback.
- System state $(R(t), P(t))^T$ models the population of RNA and protein.
- $k_R(P, t) = (b_0 \exp(-b_1(t - b_2)^2) + b_3)/(1 + (P/H)^{n_H})$
- $H = b_3 k_P/(2\gamma_R\gamma_P), \quad n_H = 1/2$

Single gene expression model



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$$\boldsymbol{S} = \begin{pmatrix} 1 & -1 & 0 & 0 \\ 0 & 0 & 1 & -1 \end{pmatrix}$$

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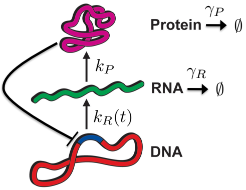

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- Deterministic MRE $\phi = (\phi_R, \phi_P)^T$

$$\begin{aligned} d\phi_R/dt &= k_R(\phi_P, t) - \gamma_R\phi_R \\ d\phi_P/dt &= k_P\phi_R - \gamma_P\phi_P \end{aligned}$$

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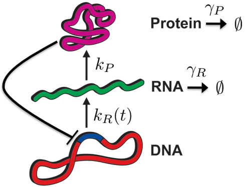

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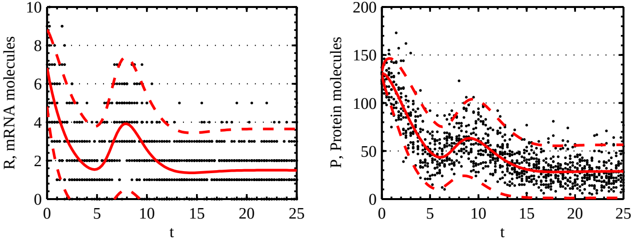
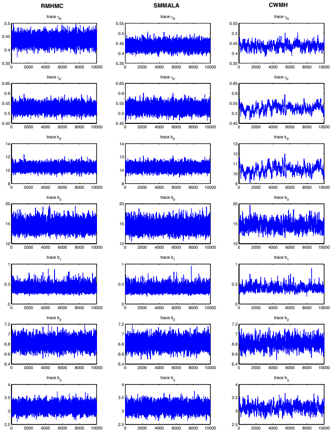
Simulated Data



- 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

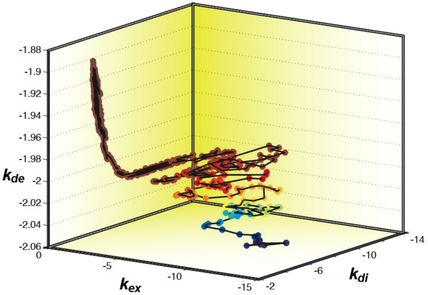
Trace Plots



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

Nonlinear Dynamic System - Circadian Clock Gene Control



Conclusions

- MJP common tool to describe many phenomena in physical and life sciences.
- LNA provides a useful approximation in appropriate operational regimes.
- Decouples deterministic and stochastic characteristics of model.
- Statistical inference remains a formidable challenge over such models.
- Exploitation of schoolboy differential geometry in MCMC provides effective inference tool.
- Phil.Trans paper describes a number of larger scale scenarios.