Dynamic Partitioning for Hybrid Simulation

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Stochastic mass action

- **Stochastic reaction rates**
  - **Kinetic constant: volume when order > 1**
  - **Combinatorial term**

$$R_r = \sum_{i=1}^{M} \alpha_{i,r} X_i \xrightarrow{k_r} \sum_{i=1}^{M} \beta_{i,r} X_i$$

$$\lambda_r(X) = \frac{k_r}{V^{\sum_{i=1}^{M} \alpha_{i,r} - 1}} \prod_{i=1}^{M} \frac{X_i!}{(X_i - \alpha_{i,r})!}$$

$$\lambda(X) = \sum_r \lambda_r(X)$$

- **Jump process dynamics**
  - **Instantaneous reactions**
  - **Next instant of reaction**
  - **Next reaction**

$$0 \le s < \tau : X_{t=s} = X_{t=0}$$

$$P_X(\tau > s) = e^{-\lambda(X)s}$$

$$P\left(X_{t=\tau} = X_{t=0} + \gamma_r\right) = \frac{\lambda_r\left(X_{t=0}\right)}{\lambda\left(X_{t=0}\right)}$$

Solution methods

- **Formal derivation**
  - Delbruck 1940, Bartholomey 58,59,62
  - McQuarrie 1963, 64
  - Peccoud & Ycart Theoretical Population Biology 1995
  - Not practical but the most simplistic models
- **Numerical solutions**
  - $P(X_t)$ solution of the master equation
  - Tractable when the state space if finite and small (10^7 states)
  - Cost is a function of the state space size
  - Finite state projection algorithm (Munsky 2006)
- **Simulations**
  - Gillespie 1976, 1977
  - Not exact – only estimates
  - Cost is a function (a^2) of accuracy (a) and intensity
  - Rare events can be missed
  - Impractical for stiff systems

Fast and slow reactions

- **Not all reactions are alike**
  - **Reactions between molecules in large numbers**
    - Deterministic mass action
    - Well approximated by ODEs
  - **All other reactions**
    - Stochastic
    - Discrete event simulation
- **Partitioning**
  - **Conditions**
    - (1): Validity
    - (2): Efficiency
  - **Iterative process**
  - **Dynamic: after every event**

$$\mathrm{R} = \mathrm{D} \cup \mathrm{C}$$

$$\forall R_{\mathrm{j}} \in \mathrm{C}: \begin{cases} (1): X_i > \gamma * |\nu_{j,i}| \\ (2): \lambda_j X > \Lambda * \lambda_{\max} \end{cases}$$

Hybrid simulation

$$dX_i = \sum_{j:R_j \in C} \nu_{j,i} \lambda_j(X)dt$$

$$P(\tau) = \lambda_{tot}(X(t+\tau))\exp\left(\int_t^{t+\tau} \lambda_{tot}(X(t')dt')\right)$$

$$\lambda_{tot}(X(t)) = \sum_{j:R_j \in D} \lambda_j(X(t))$$

$$P(j \mid \tau) = \frac{\lambda_j(X(t+\tau))}{\lambda_{tot}(X(t+\tau))}$$

$$\text{with } x \sim E(1),\ \tau : x = \int_t^{t+\tau} \lambda_{tot}(X(t')dt')$$

$$\text{with } u \sim U(0, \lambda_{tot}(X(t+\tau))), I_k = \begin{cases} 1 \text{ if } R_k \in D \\ 0 \text{ if } R_k \in C \end{cases}$$

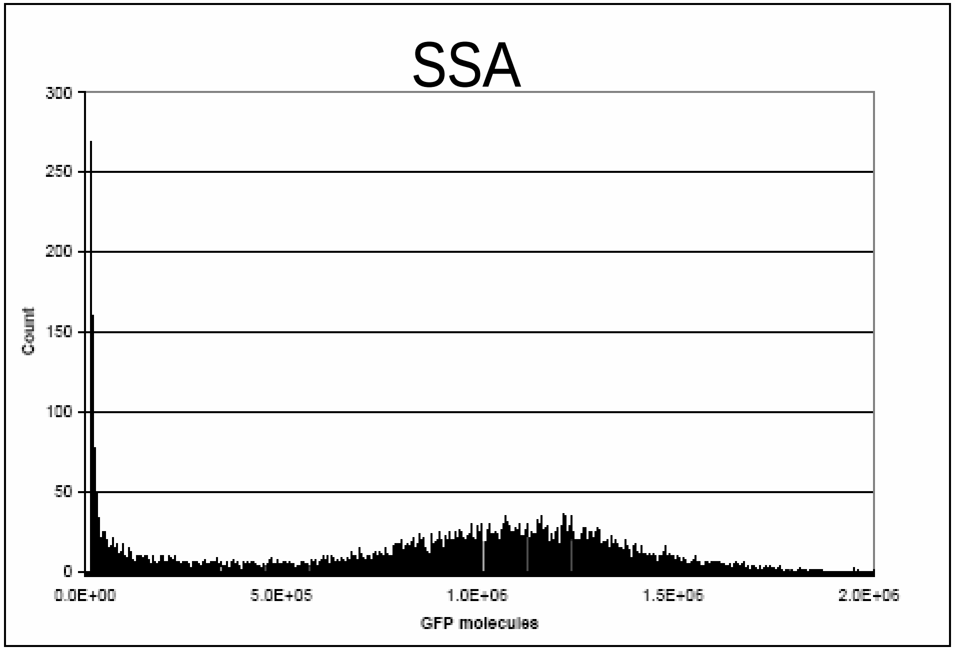
$$\sum_{k=1}^{j-1} \lambda_k(X(t+\tau))I_k \le u \le \sum_{k=1}^{j} \lambda_k(X(t+\tau))I_k$$

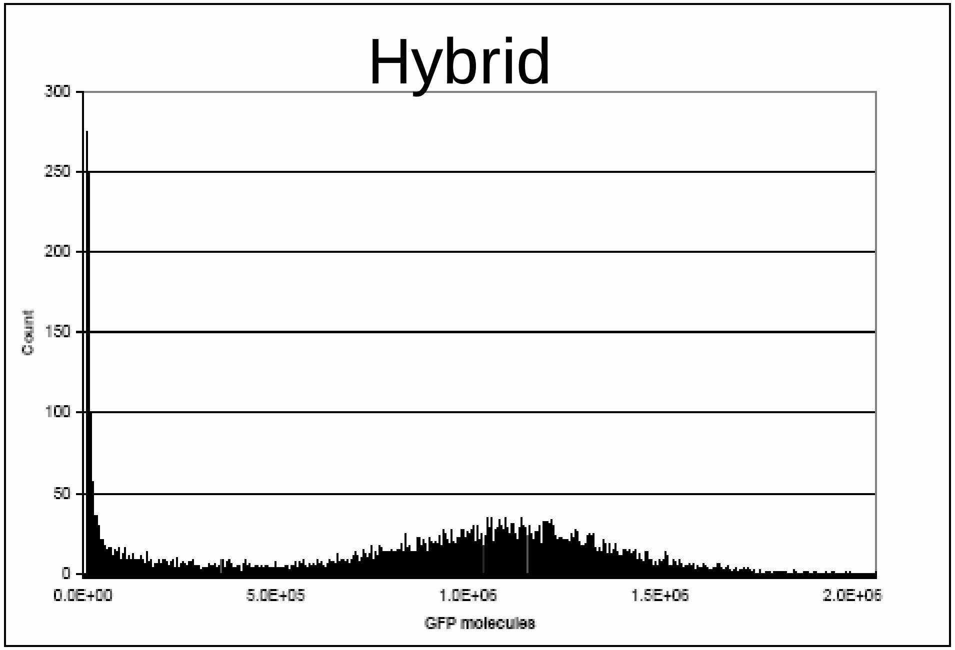
Performance

Model	Virtual Time	*Stochastic* Avg. # Events	*Stochastic* CPU Time	*Hybrid* Avg. # Events	*Hybrid* CPU Time	*S/H** Avg. # Events	*S/H** CPU Time
HIV-1 Tat *Dim* sort	1e+06 sec	561415	0.576328	4300.79	0.0652696	130.54	8.83
HIV-1 Tat *Mid* sort	1e+06 sec	4.83371e+06	4.97246	23869.7	0.359591	202.5	13.83
Intracellular viral infection	200 days	3.13796e+06	2.11551	1249.66	0.0398304	2511.05	53.11
Cycle test ($\Theta = 1000$)	100 sec	162068	0.109848	27.613	0.00267859	5869.26	41.01
Crystallization ($\Theta = 10^6$)	100 sec	454551	0.206052	110.105	0.00202239	4128.34	101.89

* S/H = Stochastic/Hybrid relative reduction in simulation cost

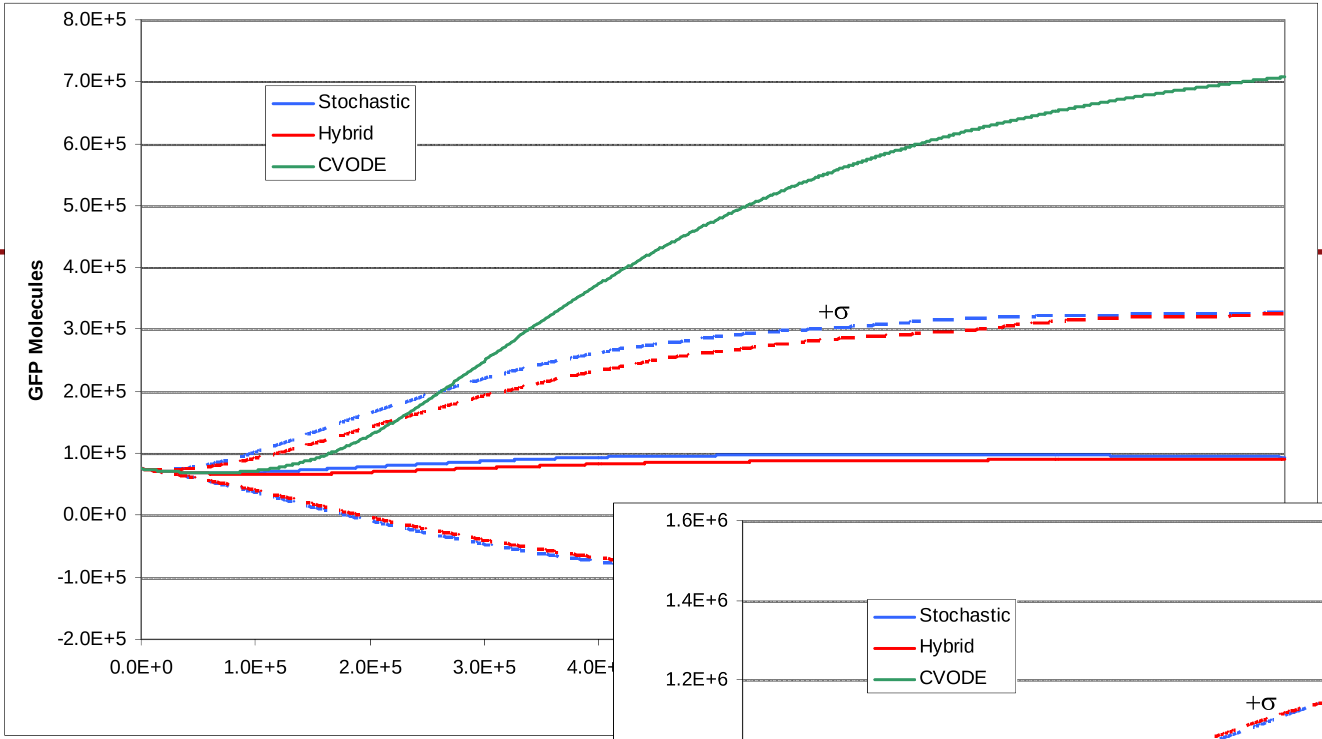
HIV-1 Tat transactivation



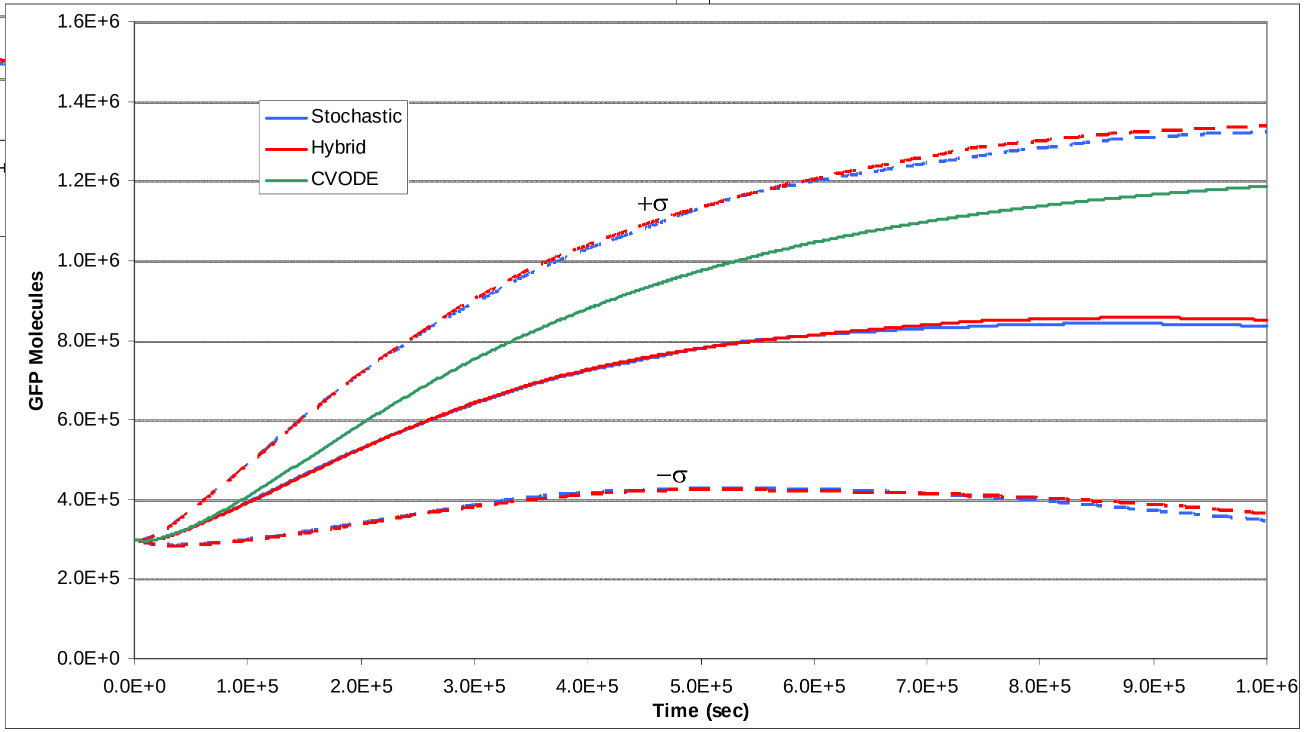


- **Positive feed-back loop**
- **ODE is bistable**
- **Stochastic is bimodal**
- **Bursts of Tat expression**
- **Change of regime**

HIV-1 Tat

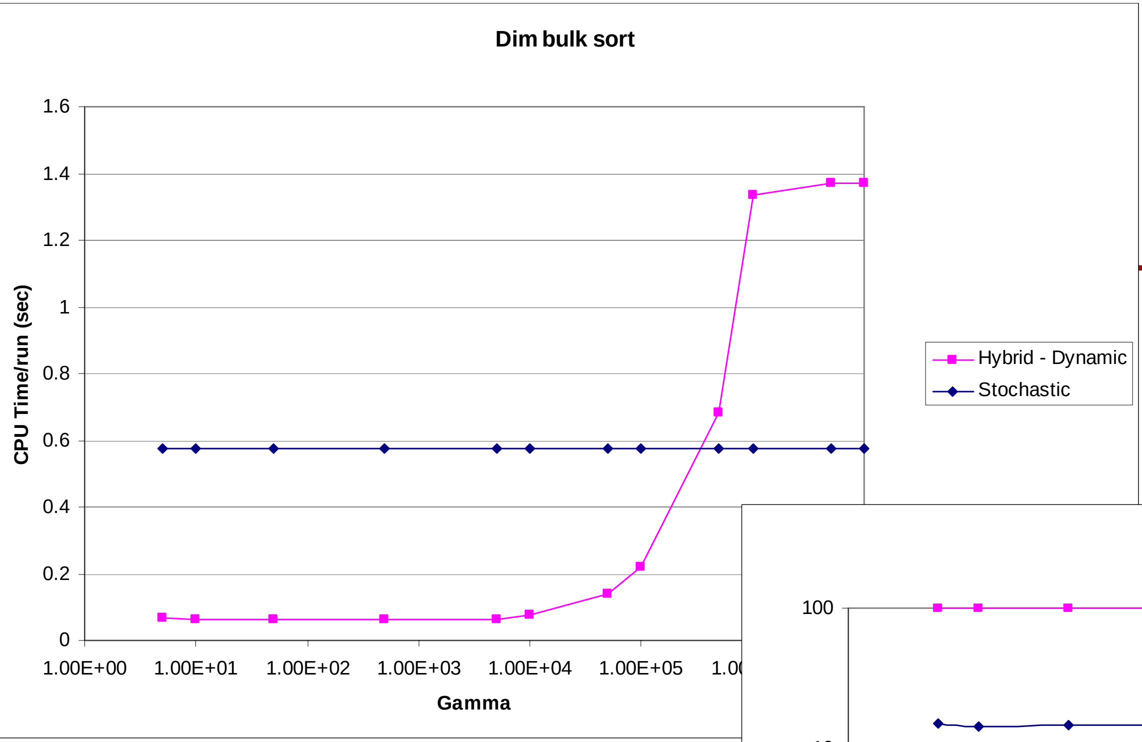


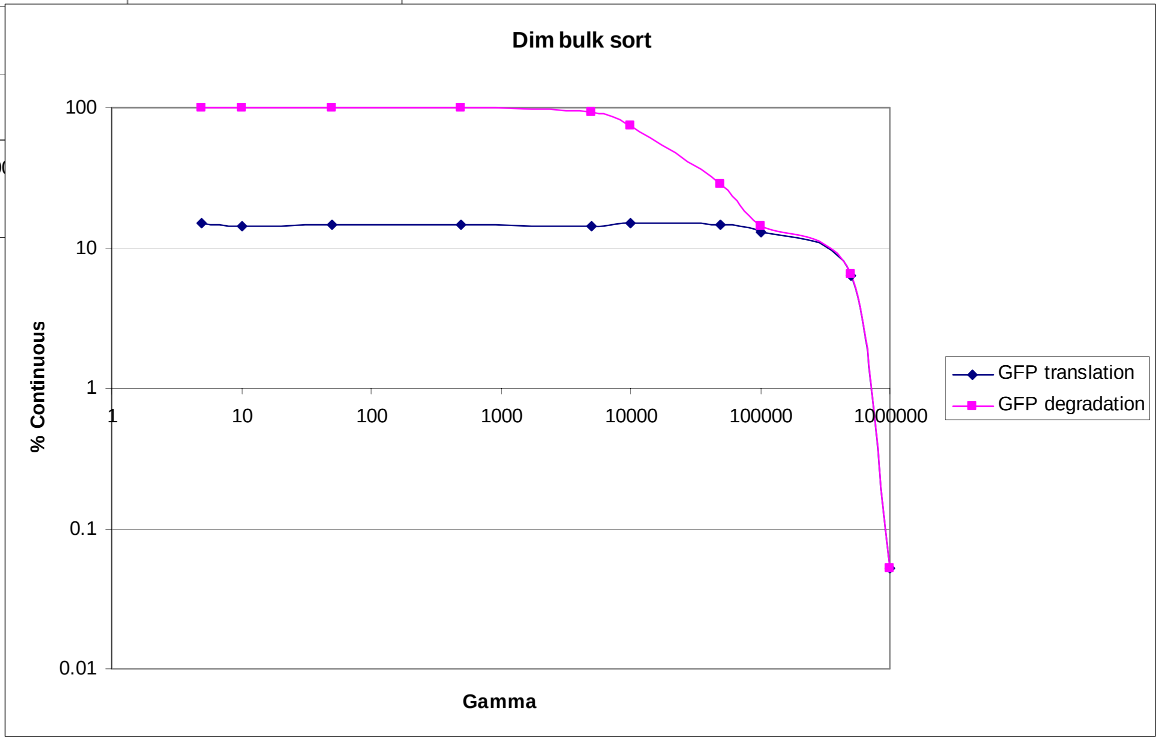
GFP Molecules
8.0E+5
7.0E+5
6.0E+5
5.0E+5
4.0E+5
3.0E+5
2.0E+5
1.0E+5
0.0E+0
-1.0E+5
-2.0E+5
0.0E+0
1.0E+5
2.0E+5
3.0E+5
Stochastic
Hybrid
CVODE
+σ



GFP Molecules
1.6E+6
1.4E+6
1.2E+6
1.0E+6
8.0E+5
6.0E+5
4.0E+5
2.0E+5
0.0E+0
0.0E+0
1.0E+5
2.0E+5
3.0E+5
4.0E+5
5.0E+5
6.0E+5
7.0E+5
8.0E+5
9.0E+5
1.0E+6
Time (sec)
Stochastic
Hybrid
CVODE
+σ
−σ

Parameter sensitivity





Software

- Applications
  - Stiff systems:
    - Gene networks and metabolic pathways
    - Bistable systems changing regimes
  - Universal simulation engine
- Current status
  - Published online in Bioinformatics (09/05/2006)
  - Command line interface (Win/Linux)
  - I/O with text files
  - **www.mobius.uiuc.edu/bioinfo06/**
- Plans
  - Make it SBML compatible
  - Make it available in various modeling environments
    - **Copasi**
    - **SimBiology**
    - **SBW**

Credits

- Collaborators
  - UIUC/CSL
    - **Bill Sanders,**
    - **Mark Griffith,**
    - **Tod Courtney**
  - Princeton:
    - **Leor Weinberger**
- Funding
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