CRITICAL OUTCOME TECHNOLOGIES INC.

Critical Outcome Technologies Inc.

Combining CART and Other Machine Learning Technologies: Evolving New Strategies for Drug Discovery and Pre-Clinical Drug Development

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President and CSO

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Accelerated Drug Discovery And Development

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OVERVIEW

- CART and TreeNET → our experience
  - Which is the “best” choice?
- *In silico* Drug Discovery:
  - HIV Integrase inhibitors
  - Why New Drugs fail
- A Glimpse of the Future of Drug Discovery
  - Improving the odds of success
- The Support Vector Like Machine (SVLM)
  - Combining the best of the best

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Basic Assumptions

- Molecular Structure --> Biological Activity
- Relationship is **Specific, Complex** and **Highly Non Linear**
- Specific Relationships can be accurately represented by an **optimal set of mathematical models**
- Entry point for all potential drugs remains ***in vitro*** screening
- Computer Hardware and **Software** exists that permit high dimensional/highly non-linear mathematical modeling in a optimal development cycle
- With sufficient and representative data ***in silico*** models can accurately **simulate** ***in vitro*** and ***in vivo*** methods

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Computational Power

- 5 Dedicated Dual Xeon processor work stations – isolated/LAN
  - 3.43 gigahertz dual processor speed
  - 4 gigabytes of RAM/machine
  - High end server connection
- 4 additional research machines
- New system development -> few days
- New system deployment -> few minutes
- Custom Applications -> few weeks

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The Modeling Options

For Advanced Molecular Structure-Activity Modeling:

CART or MART/TreeNET ->combined with

Artificial Neural Networks: PNN or GRNN or

Multivariate Adaptive Regression Splines or

Genetic Algorithm or

Support Vector Machine or

Generalized Additive-Support Vector Like Machine or

Combining the above into “Super Ensembles”

CART

- Widely used and validated Data Mining Tool in business beginning in 1980s
- More recent application to Life Sciences and Biotechnology
- Applicable to Classification and Regression problems with sufficiently large training set : Tj(x) → F*(x) as N → infinity!
- Some disadvantages but overall a robust and valuable Tool when used appropriately
- CART has been our Data Mining tool of choice since 1998

CART: Advantages

- Fast, recursive binary splitting, backward pruning algorithm
- Handles continuous, binary and categorical variables
- Handles missing values easily via surrogates
- Training Scales up well → n*N*log N
- Testing very fast → scales as Log J (# of regions)
- Always produces model summary
- Invariant to monotonic predictor variable transformations → gives the same tree model
- High degree of resistance to outliers and irrelevant predictors
- Relative variable importance provided
- Ease of use → just a few tunable parameters

CART: Limitations

- Tree Models are **Regionally Constant:**
  - Predictions constant within a given region R_j
  - Predictions can be sharply discontinuous across regions
  - Leads to potential Instability where small changes in predictors lead to dramatic changes in predictions
  - Instability likely worse for larger trees as well

- Trees **Fragment** the available data:
  - At each split daughter nodes contain fewer observations
  - Terminal nodes may contain <10 observations
  - Tree accuracy will suffer if target function requires substantial number of observations in all regions
  - Small datasets at a real disadvantage

CART: Bootstrap Re-sampling

- Most limitations addressed by Bagging many trees (hundreds)
- Lose some of the advantages of Trees but often dramatic increases in accuracy
- Generally avoid ARCing
- We only use Ensemble models based on Bagging:
  - Regression → mean of all predictions
  - Classification → simple plurality voting system

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Boosted Trees: TreeNET

- Prediction depends on linear combination of **many** small trees
  - $F_m(x) = \Sigma F_{m-1}(x) + (v * a_m) * T_m(x)$
- Constant Tree size (m = 4-10 Regions)
- Regularization →
  - "Early Stopping"/Test set
  - "Shrinkage" → v ~0.05-0.1 (Learning Rate)
  - Re-sampling

TreeNET Advantages

- Maintains all of the advantages of single CART tree except interpretability
- Scales well to large problems → n*N*LogN
- Often dramatic increase in accuracy
- Model Predictions still regionally constant but many more/smaller regions→ smaller discontinuities → improved accuracy
- Much more stable → averaging large number of trees
- Degree of data fragmentation reduced by using small trees

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CART or TreeNET?

A Few Heuristics: for Drug Discovery

- CART + Ensemble Bootstrap Re-sampling likely better:
  - Some missing values → surrogates
  - Mixture of strong > weak predictors
- MART/TreeNET likely better:
  - If data is quite limited → 10 fold cross-validation
  - Combining many weak predictors → common
- Both are strong data mining tools – choice often dependent on the data set in question
- Actual differences tend to be small and NS

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HIV Integrase Inhibitors

The Search for Orally Effective, Non-Toxic Integrase Inhibitors for the Treatment and Possible Prevention of HIV Infection Using *In Silico* Methods

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Why HIV Integrase As a Target?

3 Major HIV Enzymes/Targets identified:

- Reverse Transcriptase -> RTIs
- HIV Protease -> HIV PIs
- Current Therapy (HAART) -> combines RTI + PI
- HIV Integrase: Incorporates Viral DNA into host DNA
  - No agents currently on the market
  - Few candidates in clinical trials
  - Future optimal therapy likely to be → RT Inhibitor + Protease Inhibitor + Integrase Inhibitor
  - Potential as post exposure prophylaxis therapy
- Main problem -> identifying orally available non-toxic molecules that are BOTH potent inhibitors of HIV Integrase and effective anti-retrovirals
- Huge potential unmet economic and medical need -> viral eradication

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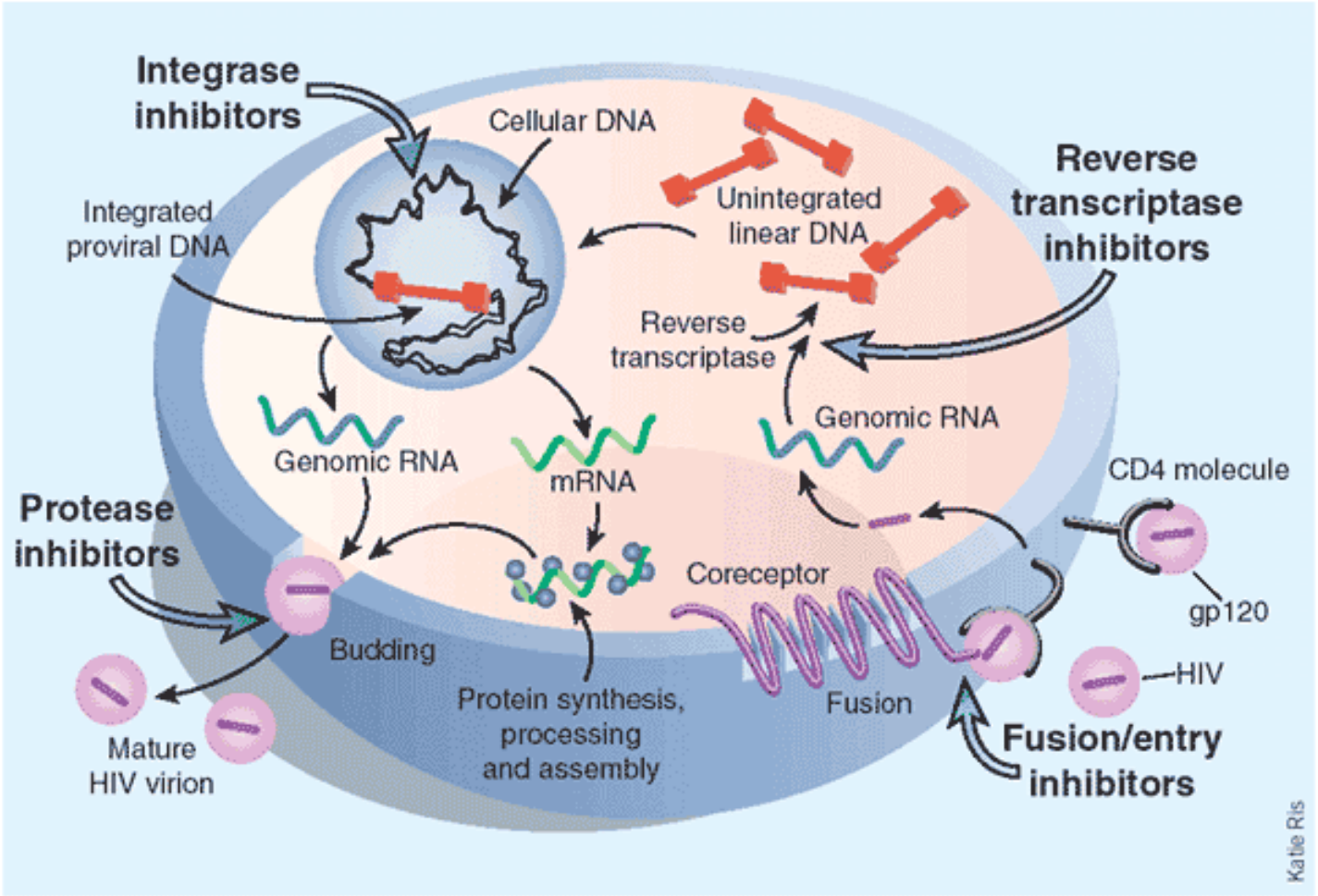
The Replication Cycle of HIV



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Creating *In Silico* Assays

First Need to Create 3 New Assays or *In Silico* Activity Filters:

1. **HIV Integrase:** **711** compounds found with *in vitro* **IC50** data for 3'Processing and Strand Transfer or unspecified "Integrase Inhibition" activity (umol/l)
2. NCI/DTP/NIAID: **2246** compounds identified with *in vitro* **anti HIV EC50** (umol/l) and
3. NCI/DTP: **1785** compounds with *in vitro* activity -> **Confirmed Active (CA) or Confirmed Inactive (CI)** -> cytoprotection assay (NOTE: CMA molecules excluded!)

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Formulating the Problem

Problems Essentially Reduced to:

2 Regression/Function Approx. Problems:

HIV Integrase Inhibition (IC50) - umol/l

Anti-retroviral Activity (EC50) - umol/l

and

1 Classification Problem:

Confirmed Active vs Confirmed Inactive

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HIV Integrase Problem (IC50)

- 711 molecular structures decomposed into 216 (largely proprietary) predictors
- Data set randomly divided into:
  - Training Set → 561 (~79%)
  - Test Set → 150 (~21%)
- CART(Bagged) → Hybrid model
  - CART output added to Training Set and Hybrid model developed as usual.
- All subsequent hybrid models developed on the Training Set and evaluated on the Test Set of 150 molecular structures in a 2 stage evaluation

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HIV Integrase (IC50) Results

Base Learner → CART/Bagging/300 Trees

Method	Test N	R^2	95% CI	p value	SD	95%CI	p value
CART	150	0.937	±0.039		0.310	±0.608	
CART+MARS	150	0.942	±0.037	NS	0.298	±0.584	NS
CART+TreeNET	150	0.939	±0.038	NS	0.310	±0.608	NS
CART+MLP	150	0.933	±0.040	NS	0.320	±0.628	NS
CART+GRNN+GA	150	0.938	±0.039	NS	0.310	±0.608	NS
CART+GA	150	0.937	±0.039	NS	0.310	±0.608	NS
CART+SVLM	150	0.937	±0.039	NS	0.314	±0.615	NS

Combining Hybrids into Super Ensemble provided no improvement over the CART+MARS model

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Anti-Retroviral Problem (EC50)

- 2246 molecular structures decomposed into 216 (largely proprietary) predictors
- Data set randomly divided into:
  - Training Set → 1796 (~80%)
  - Test Set → 450 (~20%)
- CART(Bagged) → Hybrid model
  - CART output added to Training Set and Hybrid model developed as usual.
- All subsequent hybrid models developed on the Training Set and evaluated on the Test Set of 450 molecular structures in a 2 stage evaluation

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Anti-Retroviral (EC50) Results

Base Learner → CART/Bagging/300 Trees

Model	Test N	Test R^2	Improve	Upper	Lower	pvalue	Test SD	Test 95%CI
CART	450	0.838	0.000	0.872	0.804		0.442	0.866
CART+MARS	450	0.880	0.042	0.910	0.850	NS	0.397	0.778
CART+TreeNET	450	0.898	0.060	0.926	0.870	0.048	0.352	0.689
CART+MLP	450	0.879	0.041	0.909	0.849	NS	0.381	0.747
CART+GRNN+GA	450	0.876	0.038	0.906	0.846	NS	0.387	0.759
CART+GA	450	0.885	0.047	0.914	0.856	NS	0.372	0.730
CART+SVLM	450	0.874	0.036	0.905	0.843	NS	0.293	0.574

Combining Hybrids into Super Ensemble provided no improvement over the CART+TreeNET model

CART+SVLM may be best model overall??

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Anti-Retroviral Activity

- Classification Problem: Active vs Inactive *in vitro*
- 1785 molecular structures decomposed into 216 (largely proprietary) predictors
- Active → 605 (33.9%); Inactive → 1180 (66.1%)
- Data set randomly divided into:
  - Training Set → 1435 (~80%)
  - Test Set → 350 (~20%)
- CART(Bagged) → Hybrid model
  - CART output added to Training Set and Hybrid model developed as usual.
- All subsequent hybrid models developed on the Training Set and evaluated on the Test Set of 350 molecular structures in a 2 stage evaluation

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Classification Test Results

Model	Test N	Accuracy	Sensitivity	Specificity	PPV	NPV
CART	350	88.57%	73.55%	96.51%	91.75%	87.35%
CART+TreeNet	350	87.14%	85.19%	88.02%	76.03%	93.01%
CART+ANN(PNN)+GA	350	89.14%	78.50%	94.76%	88.79%	89.30%
CART+SVM	350	88.57%	73.55%	96.51%	91.75%	87.35%
CART+SVLM	350	88.57%	89.96%	85.95%	81.89%	92.38%
TreeNET	350	89.14%	78.51%	94.76%	88.79%	89.30%
TreeNET+CART	350	86.29%	77.86%	91.32%	84.30%	87.34%
TreeNET+ANN(PNN)+GA	350	86.00%	85.95%	86.03%	76.47%	92.06%
TreeNET+SVM	350	90.57%	81.82%	95.20%	90.00%	90.83%
TreeNET+SVLM	350	88.86%	82.65%	92.14%	84.75%	90.95%

Combining Hybrids into Super Ensembles provided no improvement over the TreeNET+SVM model

Base Learner → CART/Bagging/300 Trees

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Summary of Our Experience

- Both CART and TreeNET are powerful data mining tools for Drug Discovery
- Whether CART or TreeNET is “better” depends on data set to be modeled
- CART or TreeNET hybrid models produce variable and min/modest improvements
- Hybrid SVM models may be optimal for difficult classification problems
- Super Ensembles produce no additional improvement over single best hybrid

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Why Do New Drugs Fail?

39% fail due to deficiencies in absorption, distribution, metabolism and elimination (ADME)

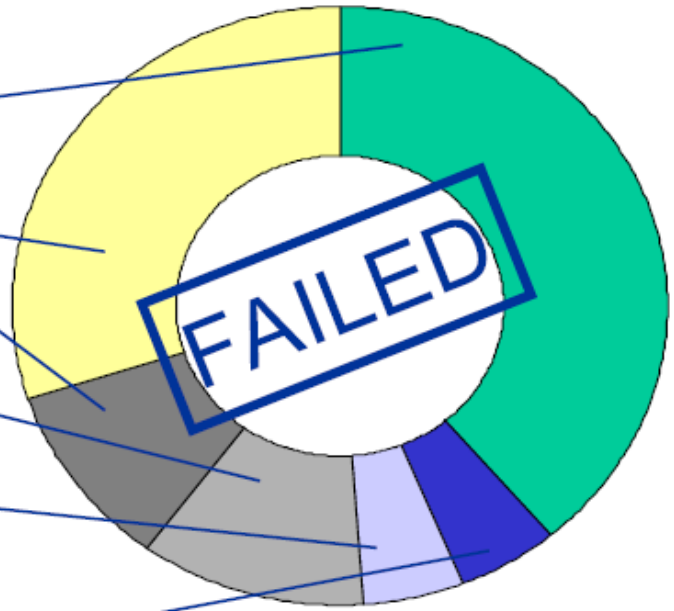
30% fail due to lack of efficacy

11% fail due to animal toxicity

10% fail due to adverse effects in man

5% fail due to commercial reasons

5% miscellaneous



Source: T.Kennedy, Drug Discovery Today, 2, 1997

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Computerized Drug Discovery

- **Next Steps** >500,000 molecules searched, >400 unique compounds designed and profiled ->
- **Efficacy:** ALL 3 criteria must be met in order to proceed!
  - Integrase Inhibition IC50 -> <10 umol/l AND
  - Anti HIV EC50 -> <10 umol/l AND
  - Classification -> Confirmed Active AND
- **HIA% / BBB penetration** AND
- **Metabolic Stability** AND
- **CYP 450 Inhibition/Induction** - > NO AND
- **Pgp** -> Substrate -> NO AND
- **Potential Toxicity:**
  - Oral rat LD50 in mg/kg AND
  - IPR mouse LD50 in mg/kg AND
  - Human MRTDD mg/kg/day AND
  - Hepatotoxicity AND
  - hERG Inhibition assay AND etc.

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Current Status – HIV Integrase Inhibitors

- *In silico* optimization completed →initial library of 13 compounds identified
- Traditional analytical chemistry completed → 170 new modified/optimized molecules
- New library + 13 original candidates → 183 underwent re-profiling/final optimization
- 12 compounds (re-optimized optimized) → Final library → awaiting synthesis
- *In vitro* HIV Integrase/anti-retroviral assays/acute toxicity → McGill University (Dr. Mark Wainberg) → Aug/Sept 2006

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In Silico Drug Development Cycle

- **Based on our experience to date**

Stage of Development	Time Line
In Silico Drug Discovery	2-3 months
Drug Synthesis	2-3 months
Confirmatory Tests	2-3 months
PK/Tox Testing*	< 9* months
Phase 1 Human Trial	3-6 months
Our Development Cycle	< 24 months
Industry Cycle	~4-6 years

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The Support Vector Like Machine

What do you get when you combine CART + the flexibility of Generalized Additive Models (GAM) + the best of SVMs + the evolutionary potential of a Genetic Algorithm?

The SVLM: a flexible tool for Classification and Regression Problems

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GAMs: T.J. Hastie and R.J. Tibshirani,1990

- Linear Models have the form:
  - Y = a+Bx,
  - a is intercept, B is slope/coefficient
- Generalized additive models (GAMs) replace x_i with a function of x_i summed over all i →
  - **$Y = a+\Sigma B_i*f_i(x_i)$ for i = 1 to P**
- Requires iterative back fitting algorithm
- Can produce very flexible nonlinear models

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Introducing:GA-SVLM

Combines features of GAMs and SVMs

1. **Function** → RBF → = $\exp(-(x_i-x')^2/(2*\sigma^2))$
   - x' → centroid → can use the mean of all x_i or search for an optimal value
   - σ^2 → width/scale → can use variance but very important to get this right
   - Epanechnikov and tri-cube kernels work too
   - If standardize data so mean = 0 and $\sigma = 1$

$$Y_j = \Sigma B_i * \exp(-(x_i-x_i')^2/(2*\sigma_i^2)) \text{ for } i = 1 \text{ to } P$$

   - **Problem**: must optimize B_i, x_i' and width (σ_i)

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GA-SVLM

2. **SVM LOSS** → Vapniks ε-insensitive loss
   - $V_\varepsilon(d) = 0$ if $|d| < \varepsilon$ otherwise $= |d| - \varepsilon$
   - Ignores errors $< \varepsilon$
   - Resistant to outliers
   - Similar type of "SPARSE" solution relying only on a portion of examples
   - Promotes good generalization
   - ε is easily estimated from training data
     - $\varepsilon \sim 3 * \sigma_{noise} * sqrt(ln(N)/N)$

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GA-SVLM

3. **SVM optimization:**
   - Minimize → $\frac{1}{2}*||B||^2+C*\Sigma V_\varepsilon(d_n)$
   - Regularization via minimizing $\frac{1}{2}*||B||^2$
   - Minimizes model complexity through smaller coefficients
   - Minimizes model error as $C*\Sigma V_\varepsilon(d_n)$ over all N examples
4. Dimension P (<=15) from CART/TreeNET data analysis – "variable importance"
5. Results in an optimized nonlinear equation (GA-SVLM) in P variables which can be examined and applied to new observations

Genetic Optimization

- Still have to determine B_i, x_i' and width (σ_i)
- Why not evolve the optimal solution using a Genetic Algorithm?
- Really just a function approximation, optimization problem with 3*P unknowns
- Think of unknowns as "chromosomes"
- Coefficients: $B_1, B_2, B_3, \ldots B_P$
- Centroids: $x'_1, x'_2, x'_3, \ldots x'_P$
- Width: $\sigma_1, \sigma_2, \sigma_3, \ldots \sigma_P$

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Genetic Optimization

- Data → Training Set +
- Genetic Algorithm (GeneHunter, WSG)
  - Genetic Operations on chromosomes
  - Time/Generations +
- Fitness Function:
  - Minimize → $\frac{1}{2}*||B||^2+C*\Sigma V_\varepsilon(d_n)$
- = GA-SVLM solution
  - **C: $Y_j = \Sigma B_i * \exp(-(x_i-x_i')^2/(2*\sigma_i^2))>=0$ then 1 otherwise -1**
  - **R: $Y_j = \Sigma B_i * \exp(-(x_i-x_i')^2/(2*\sigma_i^2))$ = real value**

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SVLM Status

- Still in development: Promising
  - Simple to construct and use
  - Performance always comparable to other methods
  - Often slightly better on difficult regression problems
- Development issues:
  - Automating estimates of SVM meta-parameters - epsilon and C
  - Optimizing choice of Kernel Function and Loss Function for data set

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When All is Said and Done

"I found the secret to happiness, but the FDA won't let me release it."

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The End..

Of Business as Usual

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