Population Models for Disease Progress and Drug Action

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Population Models for Disease Progress and Drug Action

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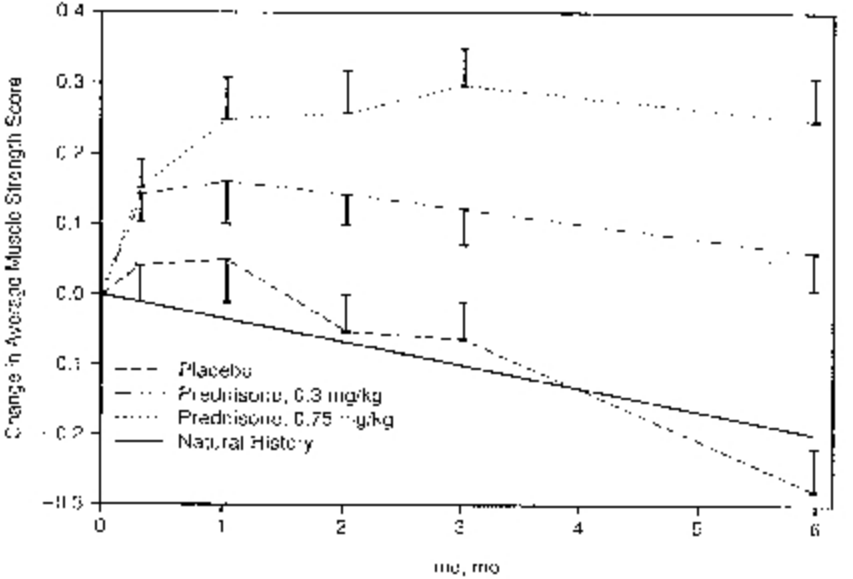
Disease Progress + Drug Action

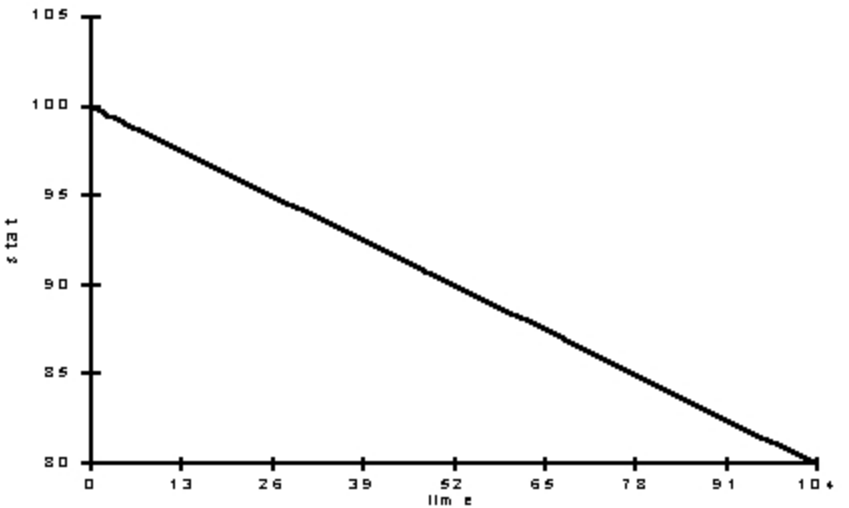
Where do Disease Progress Models Come From?

- Talk to a Disease Specialist
- Look at pictures of time course of disease
- Translate into disease progress model
- Explain the models/parameters
- Ask Disease Specialist for advice on factors influencing parameters
- Translate into models of parameters



Griggs et al. Prednisone in Duchenne Dystrophy: A randomized, controlled trial defining the time course and dose response. Arch Neurol 1991;48:383-88.

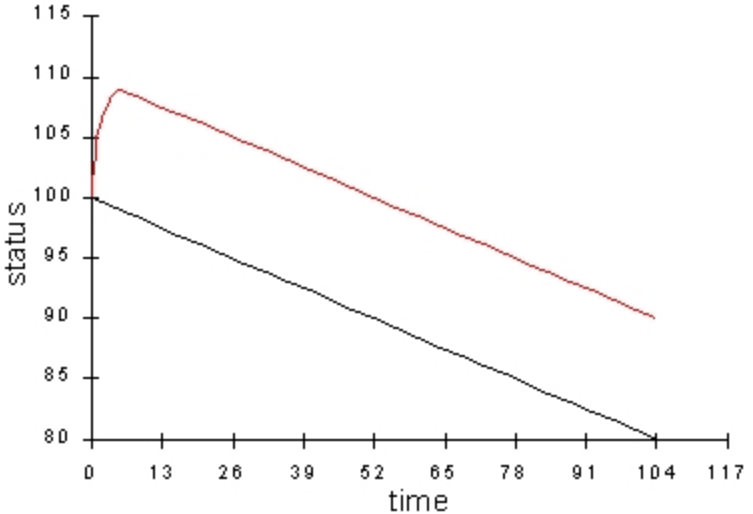
Linear Disease Progress Model



$$S(t) = S_0 + \alpha \cdot t$$

Linear Progress Model

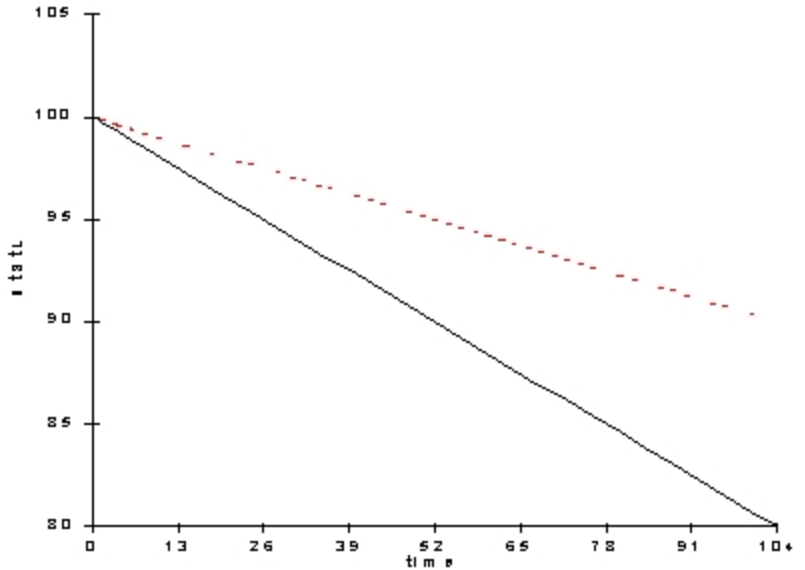
Intercept - Symptomatic Effect



$$S(t) = \left(S_0 + C_{e,A} \bullet \beta_{OFF}\right) + \alpha \cdot t$$

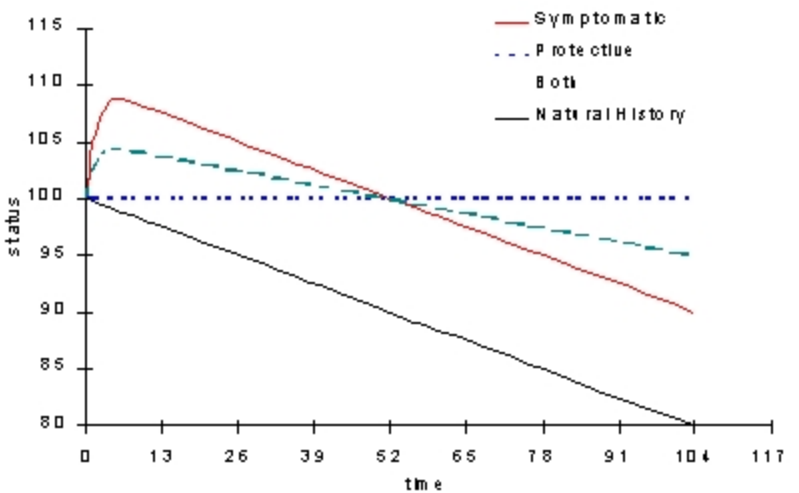
Linear Progress Model

Slope - Protective Effect



$$S(t) = S_0 + \left(C_{e,A} \bullet \beta_{SLOPE} + \alpha\right) \cdot t$$

Combined Drug Action Models



$$S(t) = S_0 + E_{OFF}(C_{e,A}) + \left(E_{SLOPE}(C_{e,A}) + \alpha\right) \cdot t$$

Asymptotic Progress Model

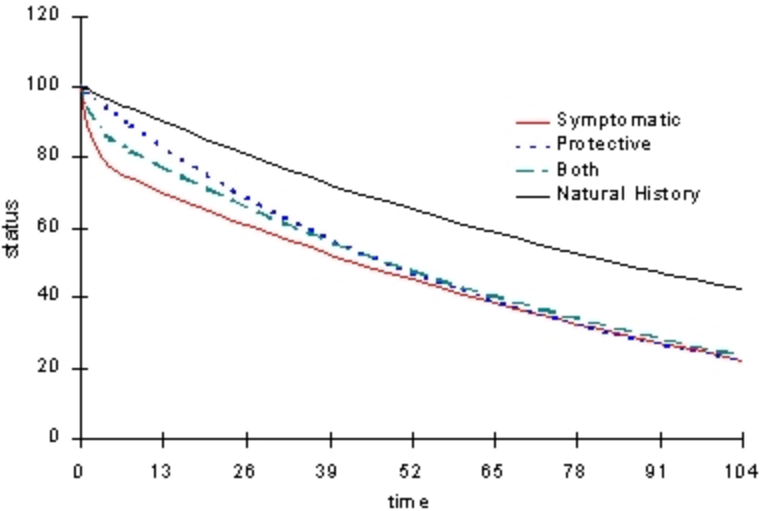
- Zero Asymptote (S_0, TP)
  - Spontaneous recovery

$$S(t) = S_0 \bullet e^{-\ln(2)/TP \bullet t}$$

- Non-Zero Asymptote (S_{ss}, TP)
  - Progression to "burnt out" state

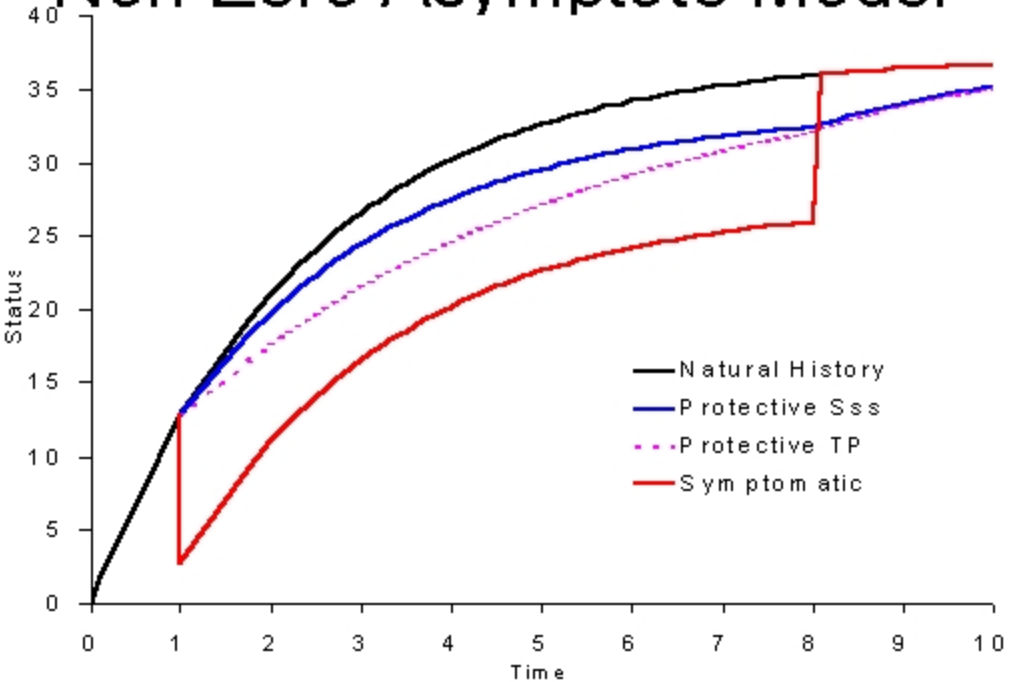
$$S(t) = S_{ss} \bullet \left(1 - e^{-\ln(2)/TP \bullet t}\right)$$

Zero Asymptote Model



$$S(t) = E_{OFF}(C_{e,A}) + S_0 \bullet e^{-\ln(2)/(E_{TP}(C_{e,A})+TP_0)\bullet t}$$

Non-Zero Asymptote Model



$$S(t) = E_{OFF}(C_{e,A}) + S_0 \bullet e^{-\ln(2)(E_m(C_{e,A})+TP_0)\bullet t} + (E_{SS}(C_{e,A}) + S_{ss,0}) \bullet \left(1 - e^{-\ln(2)(E_m(C_{e,A})+TP_0)\bullet t}\right)$$

Disease Progress Models

- Alzheimer's Disease
  - Linear: Drug effect symptomatic
- Diabetic Neuropathy
  - Linear: Drug effect both?
- Osteoarthritis
  - Linear: Drug effect protective?
- Parkinson's Disease
  - Asymptotic: Drug effect both?