# Synchronization of Circadian Rhythms:
## an MFG Model of Jet Lag

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- Jet lag: How do cells resynchronize after travel between time zones?
- Seasoned travelers:

*jet lag is worse flying east than west* !!!

# Where did we start?

**SIAM News Magazine** article

- **Lu, Cardeña, Lee, Antonsen, Girvan, & Ott** at University of Maryland College Park, *Resynchronization of circadian oscillators and the east-west asymmetry of jet-lag*, 2016.

# Lu et al. use Kuramoto's Model

- Large number of oscillators evolving according to:

$$\frac{d\theta_i}{dt} = \omega_i + \frac{K}{N}\sum_{i=1}^{N} \sin(\theta_j - \theta_i) + F\sin(\omega_S t + \rho(t) - \theta_i)$$

- $\omega_S = \frac{2\pi}{24}$, $\bar{\omega} = \mathbb{E}[\omega_i] = \frac{2\pi}{24.5}$. Time zone angle $\rho(t) \in [0, 2\pi]$.
- Define order parameter, $z(t)$:

$$z(t) = \frac{1}{N}\sum_{i=1}^{N} e^{i[\theta_i(t) - \omega_S t - \rho(t)]}$$

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(notice $z(t)$ depends upon the empirical measure of the $\theta_i(t)$ !!!)

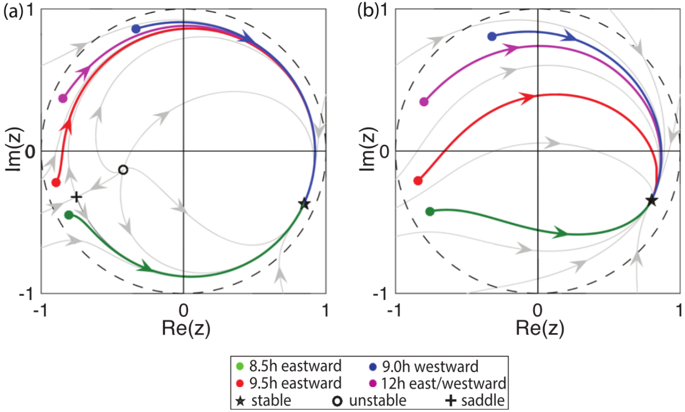
- Assuming $\omega_i$ i.i.d. & $\omega_i \sim \text{Cauchy}(\bar{\omega}, \Delta)$, in the limit $z$ satisfies:

$$\dot{z} = \frac{1}{2}\left[(Kz + F) - z^2(Kz + F)^*\right] - (\Delta + i(\omega_S - \bar{\omega}))z$$

# Stylized Facts of the Model

- An individual is entrained to their time zone if $z$ is at a stable fixed point (z(t) constant).
- Changing your time zone corresponds to a rotation of z by $\Delta\rho = p_1 - p_2$.
- The time to return to the stable fixed point can be identified as the time to recover from jet lag.
- **Lu et al.** try to understand the east-west asymmetry.

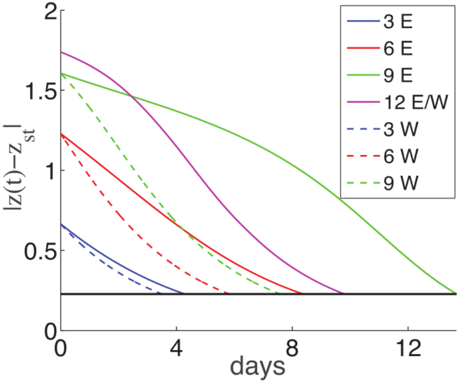
# Lu et al. Numerical Results. I




Taken from Lu et al.

# Lu et al. Numerical Results. II

Jet Lag Recovery Time




Taken from Lu et al.

# MFG Attempt at Synchronization

- **Yin, Mehta, Meyn, & Shanbhag** at University of Illinois at Urbana-Champaign, *Synchronization of coupled oscillators is a game*, 2012.

# Yin et al: Synchronization is a Game

- Each oscillator's phase evolves according to:

$$d\theta_t^i = [\bar{\omega} + \alpha_t^i]dt + \sigma dW_t^i$$

- where
  - $\boldsymbol{W}^i = (W_t^i)_{t\geq 0}$ are independent Wiener proesses
  - $\boldsymbol{\alpha}^i = (\alpha_t^i)_{t\geq 0}$ is chosen to minimize the long run average cost:

$$J^i(\boldsymbol{\alpha}^1, \cdots, \boldsymbol{\alpha}^N) = \limsup_{T\to\infty} \frac{1}{T} \int_0^T \Big[\frac{R}{2}|\alpha_t^i|^2 + \frac{1}{N}\sum_{j=1}^N \frac{1}{2}\sin^2(\frac{\theta_t^i - \theta_t^j}{2})\Big]dt$$

The second term in the integral can be written as $\bar{c}(\theta_t^i, \mu_t^N)$ with

$$\bar{c}(\theta, \mu) = \int_0^{2\pi} \frac{1}{2}\sin^2\left(\frac{\theta - \theta'}{2}\right)\mu(d\theta') \quad \text{and} \quad \mu_t^N = \frac{1}{N}\sum_{j=1}^N \delta_{\theta_t^j}$$

# Yin et al. MFG Formulation

- **Can't solve** for finite $N$, so take limit $N \to \infty$
- **Mean Field Game** formulation:
  - Fix flow $\boldsymbol{\mu} = (\mu_t)_{t \geq 0}$ of probability measures
  - the typical oscillator's phase evolves according to:

$$d\theta_t = [\bar{\omega} + \alpha_t]dt + \sigma dW_t$$

$\boldsymbol{\alpha} = (\alpha_t)_{t \geq 0}$ chosen to minimize

$$J^{\boldsymbol{\mu}}(\boldsymbol{\alpha}) = \limsup_{T \to \infty} \frac{1}{T} \int_0^T \Big[\frac{R}{2}|\alpha_t|^2 + \bar{c}(\theta_t, \mu_t)\Big] dt$$

  - and satisfies $\mu_t = \mathcal{L}(\theta_t)$ for all $t \geq 0$.

# Yin et al. MFG Formulation, cont.

The solution $(V, \lambda, \boldsymbol{\mu})$ is obtained by solving the system:

- **Hamilton-Jacobi-Bellman (HJB)** equation:

$$\partial_t V + \omega \partial_\theta V = -\frac{\sigma^2}{2}\partial^2_{\theta\theta} V + \lambda + \frac{1}{2R}(\partial_\theta V)^2 - \bar{c}(\theta, \mu_t)$$

- Fokker-Planck Kolmogorov equation:

$$\partial_t \mu_t + \omega \partial_\theta \mu_t = \frac{1}{R}\partial_\theta \left[(\partial_\theta V)\mu_t\right] + \frac{\sigma^2}{2}\partial^2_{\theta\theta}\mu_t$$

- and the asymptotic consistency for $\lambda$:

$$\lambda = \limsup_{T\to\infty} \frac{1}{T}\int_0^T \int_0^{2\pi} \left[\frac{1}{2R}(\partial_\theta V)^2 + \bar{c}(\theta_t, \mu_t)\right] \mu_t(d\theta)dt$$

# Yin et al., Numerics

- Two types of solutions:
  1. Time independent: **incoherence solution**

$$V(t,\theta) = 0 \quad \text{and} \quad \mu(t,\theta) = \frac{1}{2\pi}$$

  2. Time-periodic solutions: **traveling waves**

- Perturbation analysis by **linearization** about the incoherence solution.
  - For $R > R_c$, the incoherence solution is linearly asymptotically stable.
  - From $R = R_c$ bifurcates a family of (non-constant) traveling wave solutions.

- **No external source** (e.g. the sun).

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  2. Understand the long time behavior for oscillators that remain in the same time zone.
  3. Quantify jet lag recovery.
  4. Compare jet lag recovery for east versus west travel.

# Synchronization of Circadian Rhythms

## an Ergodic MFG Model for Staying in the same Time Zone

- Fix flow $\boldsymbol{\mu} = (\mu_t)_{t\geq 0}$ of probability measures
- The typical oscillator's phase evolves according to:

$$d\theta_t = [\bar{\omega} + \alpha_t]dt + \sigma dW_t$$

$\boldsymbol{\alpha} = (\alpha_t)_{t\geq 0}$ chosen to minimize

$$J^{\boldsymbol{\mu}}(\boldsymbol{\alpha}) = \limsup_{T\to\infty} \frac{1}{T}\int_0^T \left(\frac{R}{2}\alpha_t^2 + \bar{c}(\theta_t, \mu_t) + c_{sun}(t, \theta_t)\right) dt$$

with $\bar{c}$ as before and

$$c_{sun}(t, \theta) = \frac{F}{2}\sin^2\left(\frac{\omega_S t + \rho(t) - \theta_t}{2}\right)$$

- Finally find $\boldsymbol{\mu}$ to satisfy $\mu_t = \mathcal{L}(\theta_t)$ for all $t \geq 0$.

# HJB + FPK System

The solution $(V, \lambda, \boldsymbol{\mu})$ is obtained by solving the system:

- **Hamilton-Jacobi-Bellman (HJB)** equation:

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- and the **asymptotic consistency** for $\lambda$:

$$\lambda = \limsup_{T\to\infty} \frac{1}{T}\int_0^T \int_0^{2\pi} \left[\frac{1}{2R}(\partial_\theta V)^2 + \bar{c}(\theta_t, \mu_t) + c_{sun}(t, \theta_t)\right] \mu_t(d\theta)dt$$

# Moving Frame of Reference ($\rho(t) \equiv p$ constant)

**Change of variables:**

$$\phi = \theta - \omega_S t, \qquad \tilde{V}(t,\phi) = V(t,\theta), \qquad \tilde{\mu}_t(\phi) = \mu_t(\theta).$$

**New system:**

$$\partial_t \tilde{V} + (-\omega_S + \omega)\partial_\phi \tilde{V} = -\frac{\sigma^2}{2}\partial^2_{\phi\phi}\tilde{V} + \lambda + \frac{1}{2R}(\partial_\phi \tilde{V})^2 - \bar{c}(\phi, \tilde{\mu}_t) - c_{sun}(\phi, p)$$

$$\partial_t \tilde{\mu}_t + (-\omega_S + \omega)\partial_\phi \tilde{\mu}_t = \frac{1}{R}\partial_\phi \left[(\partial_\phi \tilde{V})\tilde{\mu}_t\right] + \frac{\sigma^2}{2}\partial^2_{\phi\phi}\tilde{\mu}_t$$

with $\bar{c}$ as before and

$$c_{sun}(\phi, p) = \frac{F}{2}\sin^2\left(\frac{\phi - p}{2}\right)$$

# Existence & Uniqueness?

- **Existence:**
  - $\bar{c}(\phi, \mu)$, and $c_{sun}(\phi, p)$ are continuous, bounded, and periodic on $[0, 2\pi]$. (**Lasry - Lions**, 2007)

- **Uniqueness:**
  - $(\phi, \mu) \hookrightarrow \bar{c}(\phi, \mu)$ is **not L-monotone**.
  - $\bar{c}(\phi, \mu) = h * \mu$ where $*$ denotes convolution.
    - $h(\phi) = \frac{1}{2}\sin^2(\phi/2)$ is **not convex**.

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- Let $\mu^*(d\phi) = \mu^{*(0)}(d\phi)$ and $V^*(\phi) = V^{*(0)}(\phi)$ be the stationary solution for $p = 0$.
- For a different time zone longitude $p$, the invariant solution is $\mu^{*(p)}(d\phi) = \mu^*(d\phi - p)$, $V^{*(p)}(\phi) = V^*(\phi - p)$.

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- $(\tilde{\mu}_t^{(p)}(d\phi))_{0 \leq t \leq T}$ finite (**as short as possible**) horizon MFG equilibrium with initial condition $\tilde{\mu}_0^{(p)}(d\phi) = \mu^*(d\phi)$.
- We expect $\lim_{t\to\infty} \tilde{\mu}_t^{(p)}(d\phi) = \mu^{*(p)}(d\phi) = \mu^*(\phi - p)$

*though we would hope that one should recover from jet-lag before $T = \infty$ !*

# Jet Lag Recovery Time

- **Definition 1**: choose $\epsilon > 0$ small and set:

$$\tau_p^1 := \inf\{t > 0 : d(\tilde{\mu}_t^{(p)}, \mu^*(\cdot - p)) < \epsilon\} \tag{2}$$

  For **east versus west travel**, we compare $\tau_p^1$ and $\tau_{-p}^1$.

- In the spirit of **Lu et al**, define:

$$z^{st} = \int_0^{2\pi} e^{i\phi} \mu^*(d\phi) \tag{3}$$

$$z_t = \int_0^{2\pi} e^{i\phi} \tilde{\mu}_t^{(p)}(d\phi) \tag{4}$$

- **Definition 2**:

$$\tau_p^2 := \inf\{t > 0 : |z_t - e^{ip} z^{st}| < \epsilon\} \tag{5}$$

# Numerical Analysis

- Numerical approximations for two problems:
  1. **Stationary solution**: $(\mu^*(d\phi), V^*(\phi))$.
     - to initialize the (finite horizon) recovery MFG
  2. **Finite Horizon Problem**:
     - with $T$ large enough to allow for jet-lag recovery

     $(\tilde{\mu}_t^{(p)}(d\phi), \tilde{V}^{(p)}(t,\phi))$ where
     $(\tilde{\mu}_0^{(p)}(d\phi), \tilde{V}^{(p)}(0,\phi)) = (\mu^*(d\phi), V^*(\phi))$.
- Naive Finite Difference Scheme:
  - Iterate HJB and Fokker-Planck-Kolmogorov.
  - Extra twist in ergodic case (no initial or terminal condition!)

# Numerical Analysis: Stationary Problem

- Unknowns: constant $\lambda$, and grid functions $\mu_j$ and $V_j$.

$$(-\omega_S+\omega+\alpha_j)(\partial_\phi V)_j+\frac{\sigma^2}{2}(\partial^2_{\phi\phi}V)_j=\lambda-\frac{R}{2}\alpha_j^2-\bar{c}(\phi,\mu)-c_{sun}(\phi,0) \tag{6}$$

$$\sum_j V_j=0 \tag{7}$$

$$\alpha_j=-\frac{1}{R}(\partial_\phi V)_j \tag{8}$$

$$(-\omega_S+\omega+\alpha_j)(\partial_\phi\mu)_j+(\partial_\phi\alpha)_j\mu_j-\frac{\sigma^2}{2}(\partial^2_{\phi\phi}\mu)_j=0 \tag{9}$$

$$\sum_j \mu_j\Delta x=1 \tag{10}$$

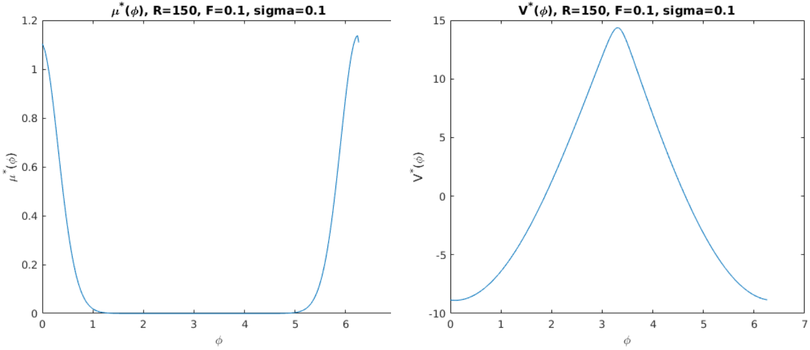
$$\mu_j\geq 0 \tag{11}$$

# Numerical Analysis: Stationary Problem

- Step 0: start with some guess for $\mu_j \approx \mu^*(\phi_j)$, and $\alpha_j$, $0 \leq j \leq N$.
- Step 1: Solve equations (6) and (7) for $V_j$ and $\lambda$. Linear system with $N+1$ equations and $N+1$ unknowns.
- Step 2: Evaluate equation (8) for $\alpha_j$.
- Step 3: Solve equations (9) and (10) for $\mu'_j$. Linear system with $N+1$ equations and $N$ unknowns.
- Repeat Steps 1 through 3 until $\lambda \approx \lambda'$, $V \approx V'$, and $\mu \approx \mu'$. More specifically,

$$\max_j \left\{ \frac{|\mu_j - \mu'_j|}{\mu'_j} : \mu'_j > \epsilon \right\} < \epsilon \tag{12}$$

# Numerical Results: Stationary Problem




(A) $\mu^*(\phi)$ (B) $V^*(\phi)$

FIGURE: Stationary Solutions

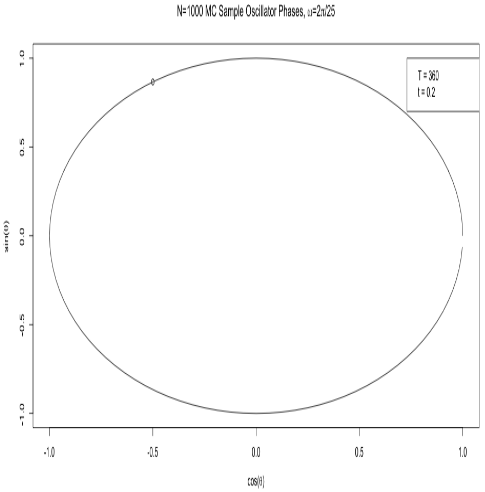
# Numerical Analysis: Finite Horizon Problem

- **Choose** horizon $T$ large enough (say 3 weeks)
- **Choose** for $\mu_0$ the invariant distribution of the original time zone
- **Choose** a flow $\boldsymbol{\mu} = (\mu_t)_{0 \le t \le T}$ consistent with $\mu_0$
- **Solve HJB**
- **Solve Fokker-Planck-Kolmogorov** with gradient of value function
- **Update** the flow $\boldsymbol{\mu}$ and iterate until fixed point is reached

**VOILA !**

# Monte Carlo Simulations

**Traveling East,** $p = 8\omega_S$, $\bar{\omega} = 2\pi/25$



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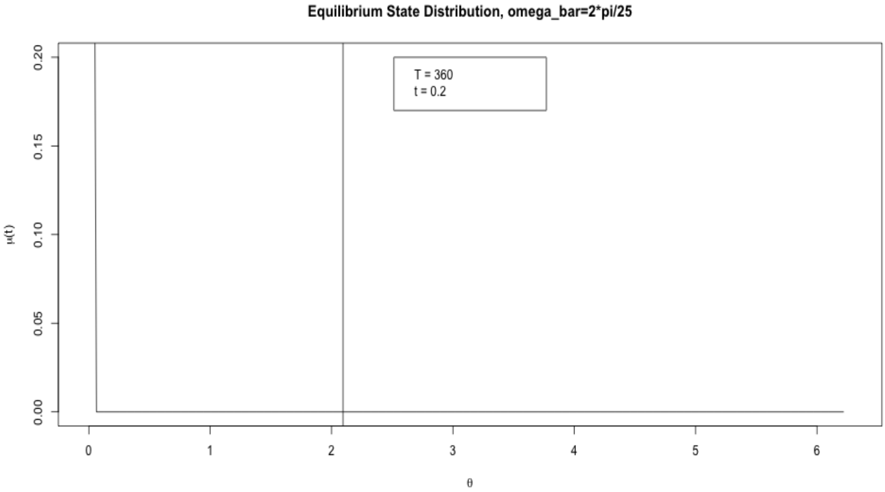

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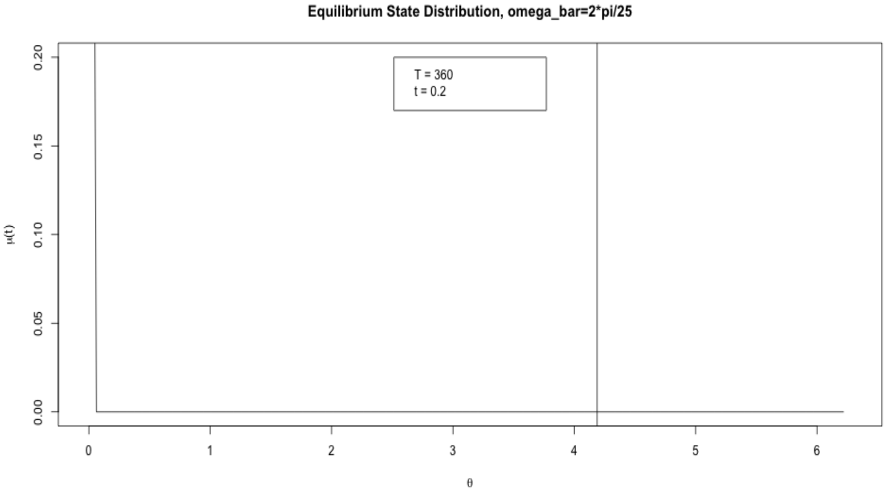
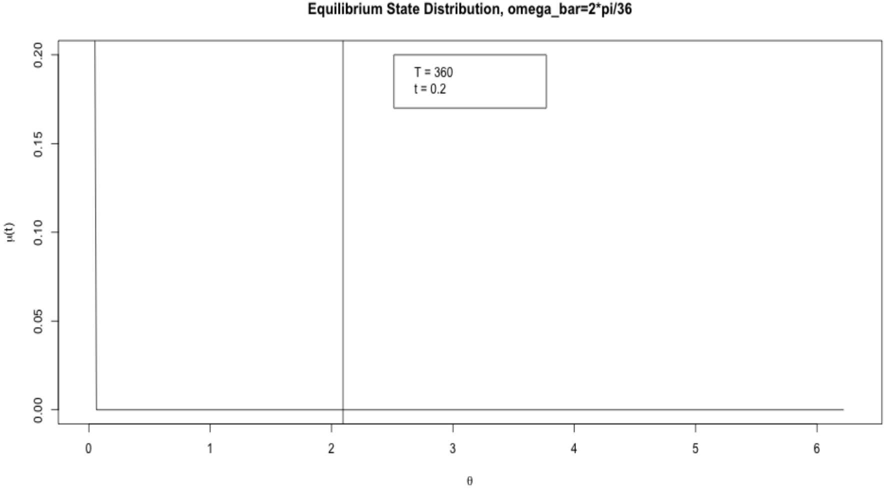
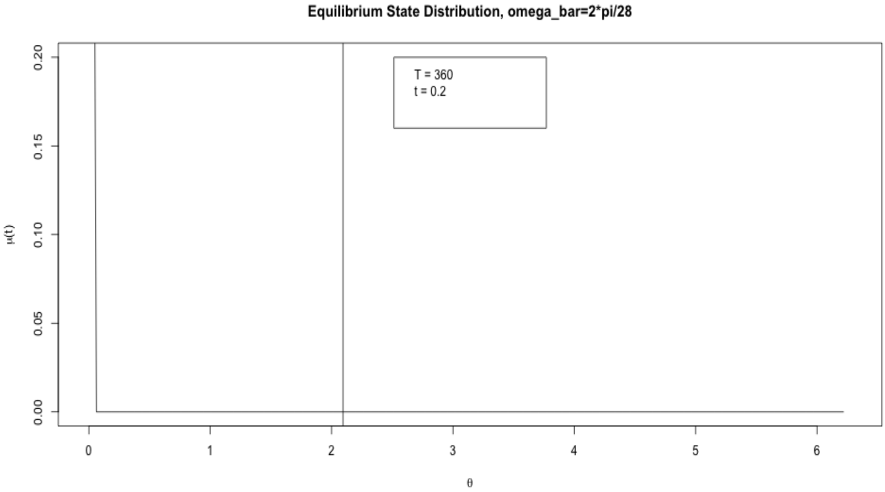


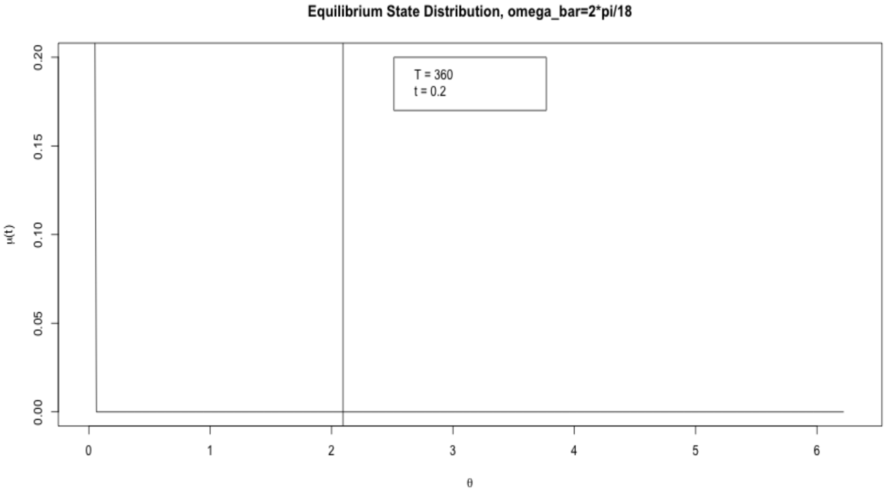
# Traveling East, $\bar{\omega} = 2\pi/36$



# Traveling East, $\bar{\omega} = 2\pi/28$



# Traveling East, $\bar{\omega} = 2\pi/18$



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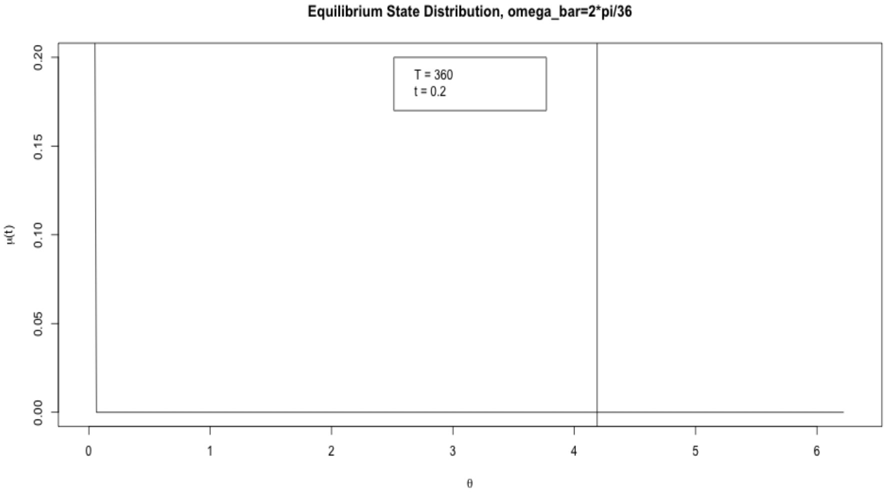

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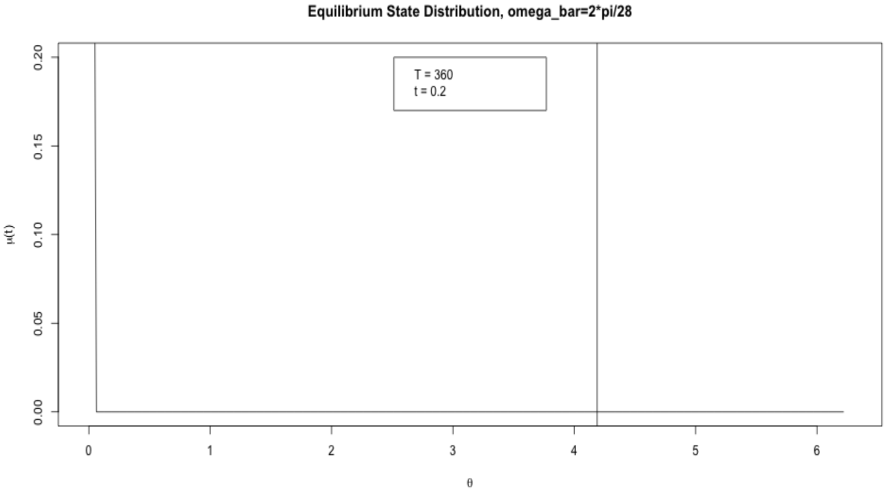

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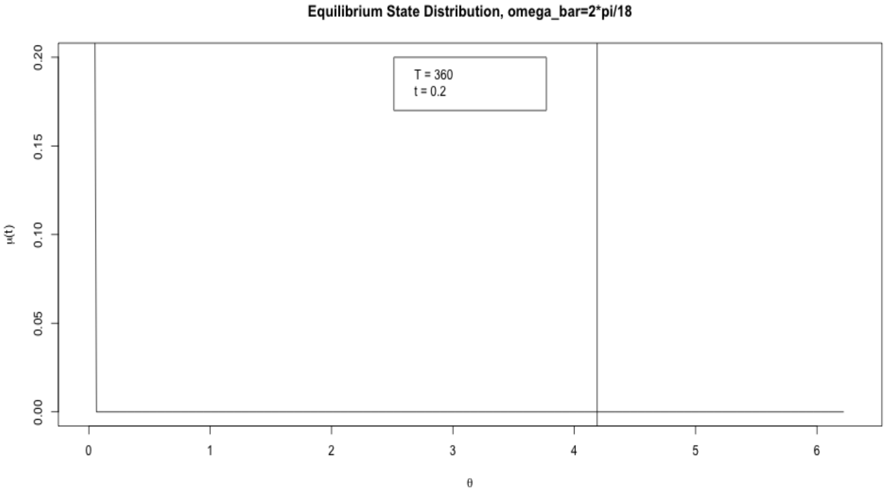

# Jet Lag Recovery Cost

- Instead of comparing the time to recover from jet lag, compare the cost associated with jet lag recovery:

$$
\begin{aligned}
f(t) &= f_\alpha(t) + f_{osc}(t) + f_{sun}(t) \\
f_\alpha(t) &= \int_0^{2\pi} \left(\frac{R}{2}\alpha(t,\phi)^2\right) \tilde{\mu}^{(p)}(t, d\phi) \\
f_{osc}(t) &= \int_0^{2\pi} \bar{c}(\phi, \tilde{\mu}^{(p)}(t,\cdot))\tilde{\mu}^{(p)}(t, d\phi) \\
f_{sun}(t) &= \int_0^{2\pi} c_{sun}(\phi)\tilde{\mu}^{(p)}(t, d\phi)
\end{aligned}
\tag{13}
$$

- Note: $\lim_{t\to\infty} f(t) = \lambda$

# Numerical Results: Jet Lag Recovery Cost

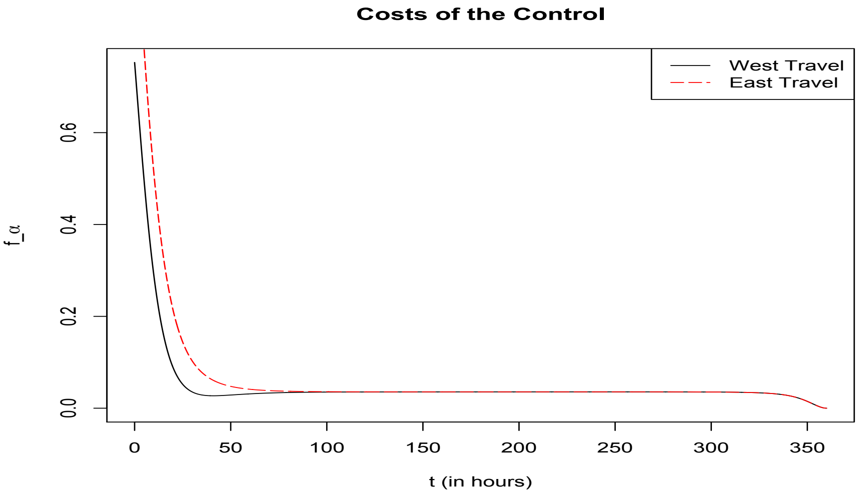


FIGURE: $f_\alpha(t)$

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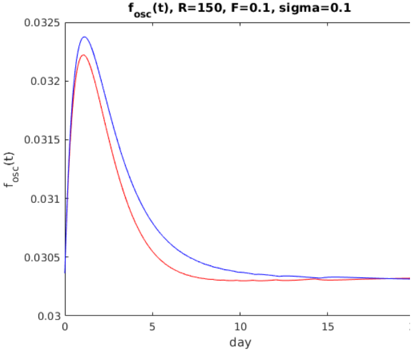
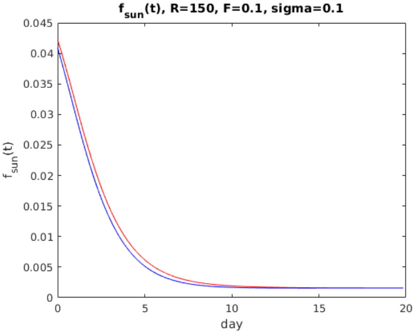



(A) $f_{osc}(t)$




(B) $f_{sun}(t)$

FIGURE: Eastward travel in red. Westward travel in blue. 9 time zones.

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- Preliminary results: we just **scratched the surface** !

# Realistic Challenges

- **Factors affecting circadian rhythm:**
  - Irregular work and sleep schedules.
  - Bodily hormones.
  - **Sunlight exposure**
- **Factors affecting the feeling of jet lag**
  - Traveling is terrible (crowded, low air pressure, time consuming).
  - **Traveling during the day or night**
  - Returning home versus traveling somewhere foreign.
- **Identification of the Model Parameters**
  - $R$, $F$, and $\sigma$ are difficult to identify
  - $R$, $F$, and $\sigma$ change from an individual to another.

# Remark about Uniqueness

- Because

$$\bar{c}(\phi, \mu) = h * \mu \quad \text{with} \quad h(\phi) = \frac{1}{2}\sin^2(\phi/2)$$

  we can write the problem as a potential game:
- Which can be solved as the optimal control of a McKV SDE
- Existence and uniqueness of a solution if $h$ is
  - even
  - twice continuously differentiable
  - convex
- The only missing requirement is convexity.
  - the only periodic convex function is a constant!