

CONCENTRATION DRIFT AND RATE-DEPENDENT RESTITUTION IN THE CRN ATRIAL MEMBRANE MODEL

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ATRIAL MEMBRANE MODEL

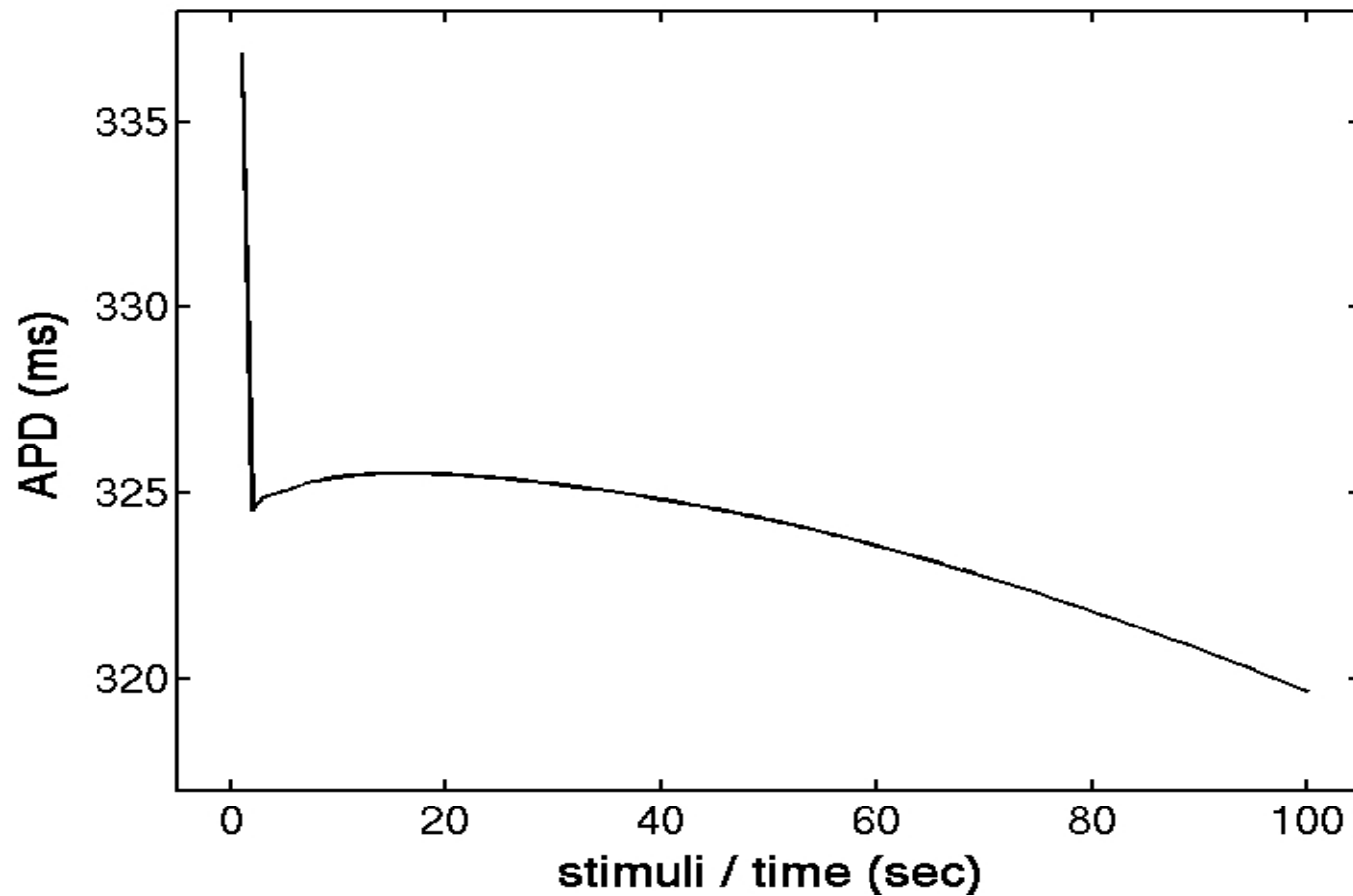
- Courtemanche, Ramirez, Nattel (CRN)
- published in 1998
- based on human data where available
- intracellular Na and K concentrations ($[Na]_i$ and $[K]_i$) are state variables
- background Na current and Na-K pump current adjusted so intracellular Na and K EQUILIBRATE AT REST

PRELIMINARY RESULTS - DRIFT

- during pacing at constant rate, action potential duration (APD), $[\text{Na}]_i$, and $[\text{K}]_i$ drifted
- without pacing (at rest), $[\text{Na}]_i$ and $[\text{K}]_i$ drifted
- to eliminate drift at rest, adjusted background Na current and Na-K current conductances by approximately 2% and 1%, respectively

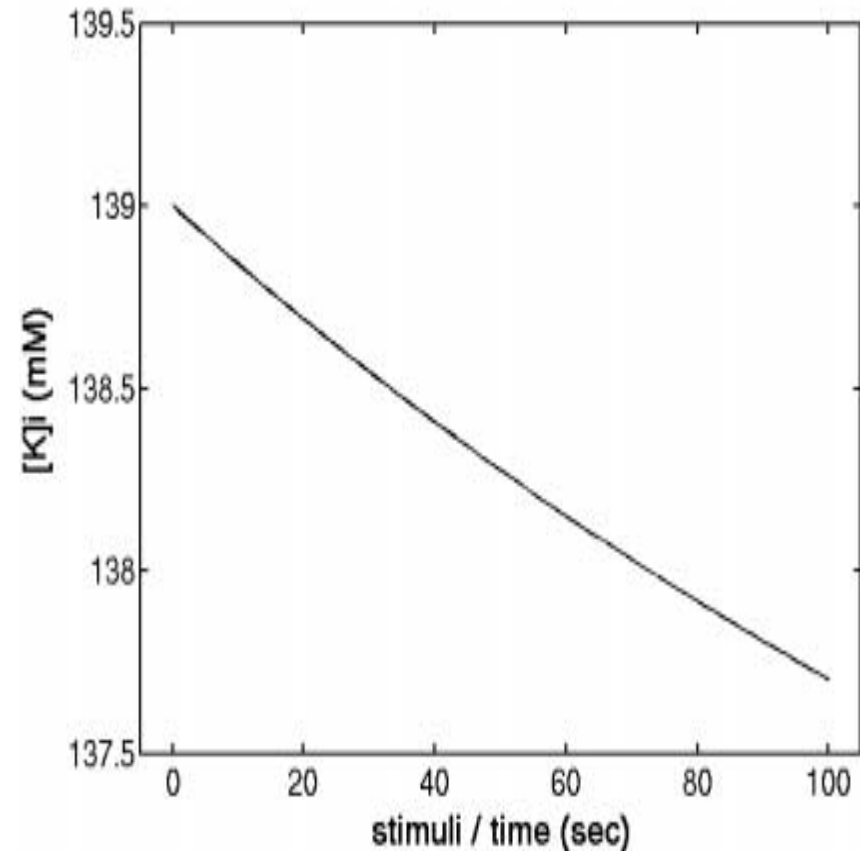
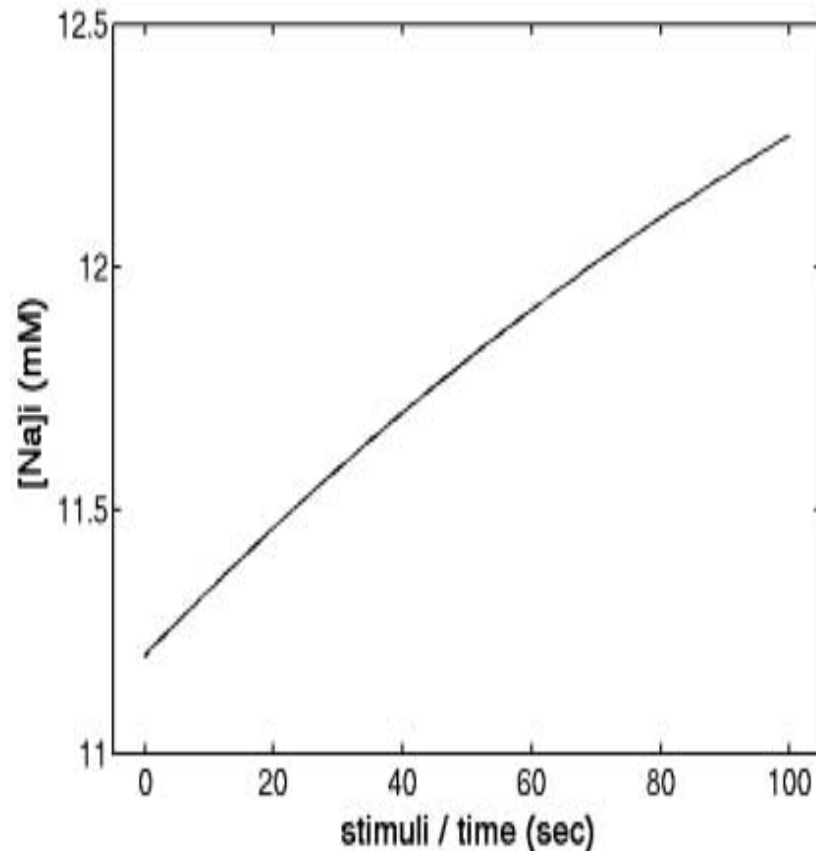
DRIIFT DURING PACING

- paced membrane at basic cycle length (BCL) of 1000 ms
- APD drifted



DRIFT DURING PACING - CONT.

- paced patch at basic cycle length (BCL) of 1000 ms
- $[Na]_i$, $[K]_i$ drifted

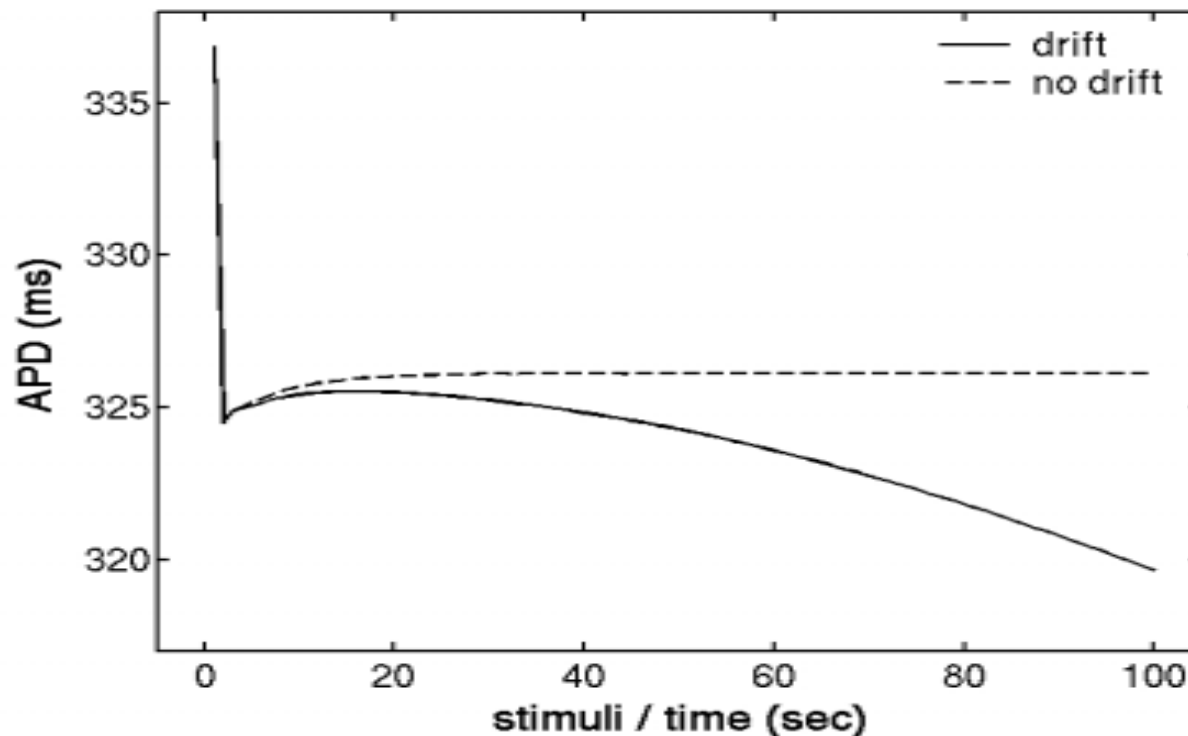


DRIFT IN IONIC MODELS

- DiFrancesco-Noble model
 - Guan et al.
 - defect in model due to concentration drift
 - defect eliminated by fixing concentrations
- Luo-Rudy-Dynamic model
 - Hund et al.
 - found APD, $[Na]_i$ and $[K]_i$ drifted
 - eliminated by assigning ion carrier to stimulus
- CRN model
 - Courtemanche et al.
 - acknowledge drift may occur

ELIMINATE APD DRIFT

- tried all combinations of:
 - fixing $[\text{Na}]_i$ or $[\text{K}]_i$
 - making stimulus charge be carried by Na^+ or K^+ ions
- only successful when $[\text{Na}]_i$ and $[\text{K}]_i$ was fixed

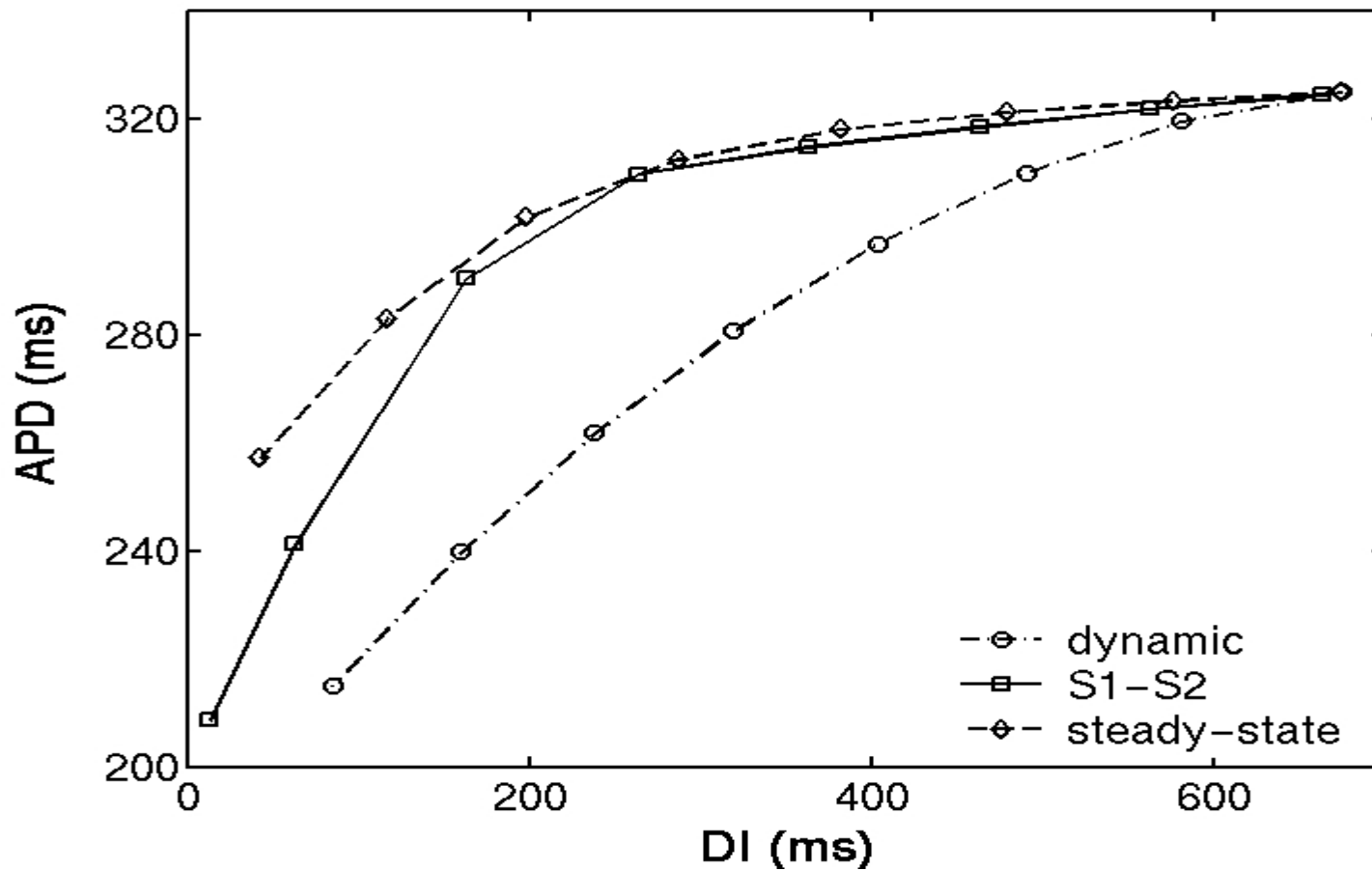


PACING PROTOCOLS

- S1-S2
 - initial condition for each coupling interval was rest
 - applied S1 and S2 with varying coupling intervals (CIs)
 - measured diastolic interval (DI) and APD at each CI
- STEADY-STATE
 - initial condition for each BCL was rest
 - paced at BCLs of 300, 400, 500, ... , 1000 ms
 - measured steady-state DI and APD for each BCL
- DYNAMIC
 - initial condition was rest
 - applied 50 stimuli at 1000 ms, measured last 5 DI and APD
 - sequentially changed BCL to 900, 800, ... , 300 ms
 - measured last 5 DI and APD at each BCL

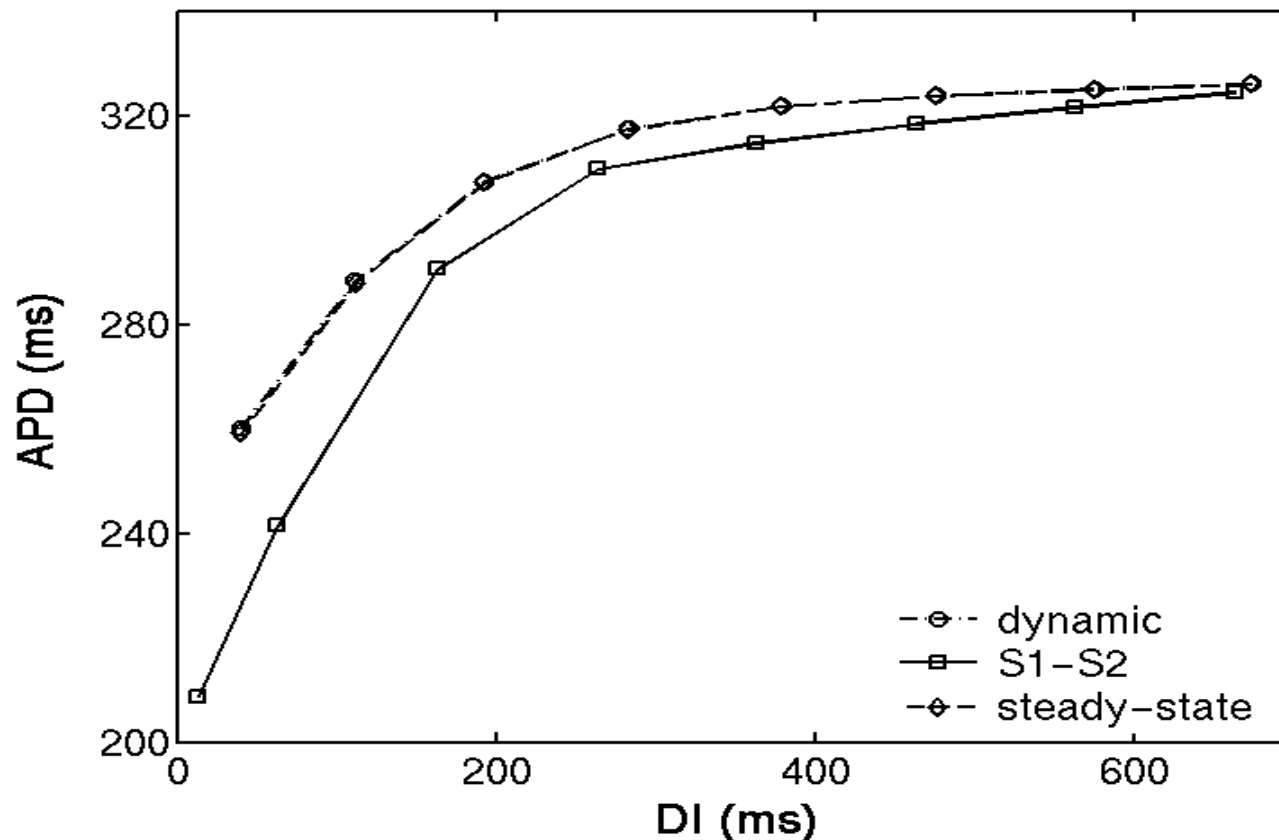
DRIFT APD RESTITUTION

- DRIFT = allowed $[\text{Na}]_i$ and $[\text{K}]_i$ to vary
- markedly different particularly at short DI



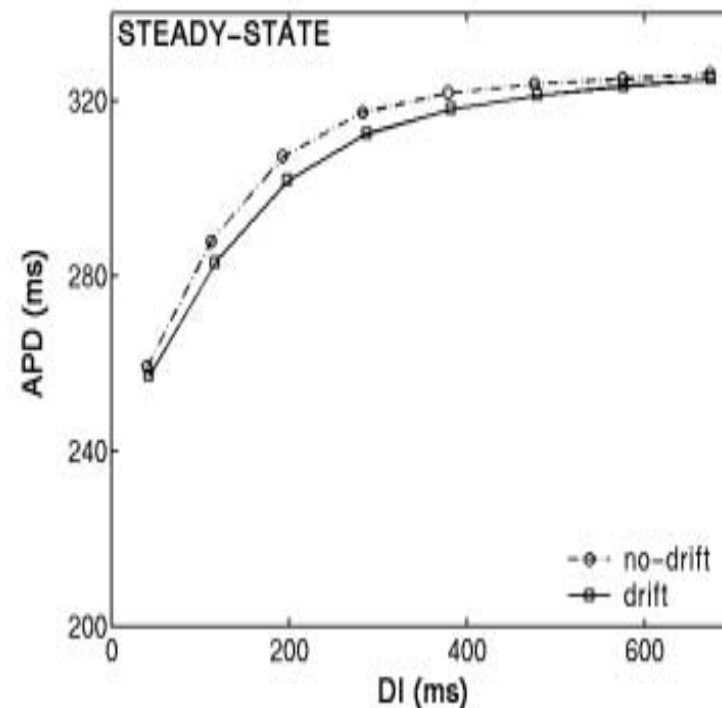
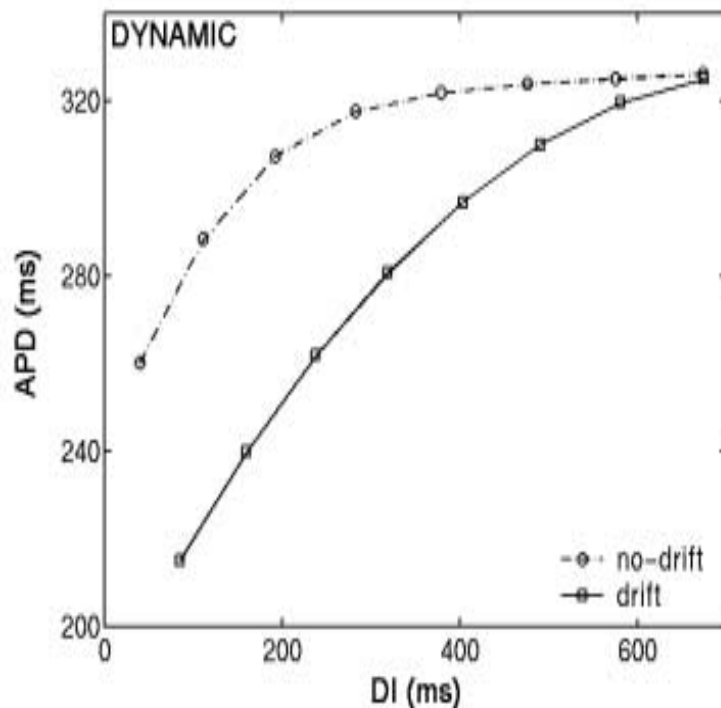
NO-DRIFT APD RESTITUTION

- NO-DRIFT = fixed $[Na]_i$ and $[K]_i$
- dynamic and steady-state virtually identical
- S1-S2 markedly different at short DI



COMPARISON WITH AND WITHOUT DRIFT

- S1-S2: identical
- dynamic: markedly different
- steady-state: only slightly different



CONCLUSIONS

- pacing protocol has pronounced effect on restitution
 - quantitative and qualitative differences in curves
 - shape and slope of curves affected
- effect is enhanced by concentration drift
- for a given protocol effect of drift varies
- PACING PROTOCOL AND CONCENTRATION DRIFT HAVE A SIGNIFICANT EFFECT ON APD RESTITUTION AND MUST BE CONSIDERED
- CONCENTRATION DRIFT COULD HAVE A SIGNIFICANT EFFECT ON LONG-TERM MEMBRANE DYNAMICS AND MUST BE CONSIDERED DURING PACING STUDIES